MEDICAL LIBRARY

Vol. 219 No. 2 FEBRUARY, 1950 No. 935

FEB 23 1950

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

REG. U. S. PAT. OFF.
ESTABLISHED 1820

Editor: E. B. KRUMBHAAR, M.D.

Associate Editors: RICHARD A. KERN, M.D. WILLIAM C. STADIE, M.D.

W. Lloyd Aycock, Carl Bachman, Herman Beerman, Wm. L. Benedict, Frank B. Block, George E. Burch, Stuart K. Bush, G. Lyman Duff, Franklin G. Ebaugh, Cary Eggleston, Noah D. Fabricant, Harry Gold, John E. Gordon, N. R. Ingraham, Jr., C. G. Johnston, Russell H. Morgan, H. P. Wagener, Irving J. Wolman, E. G. D. Murray, I. S. Ravdin, John F. Roach, John H. Stokes

Experiences with Venous Thrombosis and Pulmonary Embolism, with Special Reference to Anticoagulant Therapy. By JOSEPH B. VANDER VEER, M.D., P. T. KUO, M.D., and DAVID S. MARSHALL, II, M.D. 117

Two-Year Follow Up Report of Patients with Miliary and Meningeal Tuberculosis Treated with Streptomycin. By PAUL A. BUNN, M.D. 127

The Effect of Dibutoline Sulfate on Interdigestive Gastric Secretion of Peptic Ulcer Patients. By STANLEY H. LORBER, M.D., and THOMAS E. MACHELLA, M.D. 133

Clinical Experience with Thiomerin. By CHARLES D. ENSELBERG, M.D., and HENRY G. SIMMONS, M.D. 139

Use of Hyaluronidase in Preventing the Pain of Subcutaneous Heparin Injection. By M. S. TUCHMAN, M.D., and S. E. MOOLTEN, M.D. 147

The Etiology of Pulmonary Arteriolosclerosis (Ayerza's Syndrome). By SIMON S. LEOPOLD, M.D. 152

Glucose Tolerance: 1. A Comparison of 4 Types of Diagnostic Tests in 103 Control Subjects and 26 Patients with Diabetes. By JOHN H. MOYER, M.D., and C. RAY WOMACK, M.D. 161

Diagnostic Value of Histologic Lesions of Striated Muscle in Rheumatoid Arthritis. By LEON SOKOLOFF, M.D., SIGMUND L. WILENS, M.D., JOSEPH J. BUNIM, M.D., and CURRIER MCEWEN, M.D. 174

The Role of Lipid Deposition in Renal Arteriolar Sclerosis. By S. L. WILENS, M.D., and S. K. ELSTER, M.D. 183

Lipotropic Effect of Liver Extract and Other Supplements in Dietary Induced Liver Injury in Rats. By VICTOR A. DRILL, Ph.D., M.D., and CHARLES A. HALL, M.D. 197

Eosinophilia in Infectious Mononucleosis. By ROBERT E. KAUFFMAN, M.D. 206

Progress of Medical Science

Ophthalmology. WILLIAM L. BENEDICT, M.D., and HENRY P. WAGENER, M.D. 209

Surgery. I. S. RAVDIN, B.S., M.D., and C. G. JOHNSTON, M.S., M.D. 219

Proceedings of the Physiological Society of Philadelphia 228

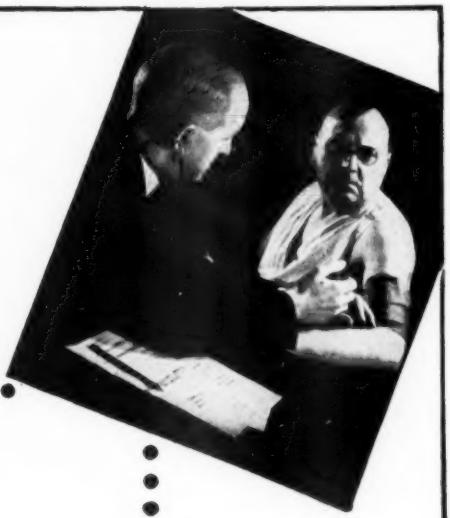
Complete contents on adv. page 10

OWNERS AND PUBLISHERS LEA & FEBIGER PHILADELPHIA 6, PENNA.

COPYRIGHT, 1950, BY LEA & FEBIGER. ALL RIGHTS RESERVED. ENTERED AS SECOND CLASS MATTER NOVEMBER 5, 1887 AT THE POST OFFICE AT PHILADELPHIA, PA. UNDER THE ACT OF MARCH 3, 1879

PUBLISHED MONTHLY. SUBSCRIPTIONS, TEN DOLLARS A YEAR

YOUR "SPHYG" TELLS THE CLINICAL STORY



Seeing is believing in the treatment of vascular hypertension. Your own sphygmomanometer shows what Hepvisc can do in reducing blood pressure.

Hepvisc is a synergistic combination of two useful hypotensive drugs; namely, hexanitrate of mannitol and viscum album extract. Clinical studies and also pharmacological tests on cats show substantial reductions of blood pressure with its use.

Hypertensive headaches are relieved by Hepvisc.

HEPVISC
Reg. U. S. Pat. Off.
Hexanitrate of Mannitol plus Viscum Album Extract

Supplied in Bottles of 50-500-1000 tablets.

AVAILABLE AT ALL DRUG STORES

COMPOSITION
Each tablet contains 6 mg. hexanitrate of mannitol and 50 mg. solid extract viscum album.

DOSAGE
2 tablets three or four times daily as needed.

Complete Literature and Professional Samples Sent upon Request

ANGLO-FRENCH LABORATORIES, INC.

75 VARICK STREET, NEW YORK 13, N. Y.

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

FEBRUARY, 1950

ORIGINAL ARTICLES

EXPERIENCES WITH VENOUS THROMBOSIS AND PULMONARY EMBOLISM, WITH SPECIAL REFERENCE TO ANTICOAGULANT THERAPY

By Joseph B. Vander Veer, M.D.

P. T. Kuo, M.D.

AND

David S. Marshall, II, M.D.

PHILADELPHIA, PENNSYLVANIA

(From the Department of Cardiology, Division of Medicine, Pennsylvania Hospital)

During the past decade the problem of venous thrombosis and pulmonary embolism has been the object of much interest and investigation. Many significant contributions including more scientific methods of treatment of thrombo-embolic diseases have been made. In spite of these studies, a number of controversial points concerning pathogenesis, diagnosis and treatment still require clarification. The purpose of this report is: 1, to show the high incidence with which thrombo-embolism is seen among patients in a general hospital; 2, to stimulate general alertness for venous thrombosis located outside of the lower extremities; 3, to stress the importance of maintaining an effective prothrombin time level in patients under Dicumarol therapy; 4, to compare the results of anticoagulant therapy with other methods of treatment; and, 5, to suggest a modified form of prophylactic anticoagulant program aimed at bringing the mortality rate of thrombosis and embolism to a minimum.

Material and Method of Study. Since January, 1947, patients admitted to the Pennsylvania Hospital with clinical evidence of venous thrombosis and, or, pulmonary embolism have been seen in emergency consultation by members of the peripheral vascular section of the surgical department and cardiovascular section of the medical department. The method of treatment best suited for the individual patient was carried out. A total of 222 patients have been followed in a 27-month period. The cases are divided into 3 groups according to the method of therapy employed:

Group 1. Patients Treated with Anticoagulants. The patients of this group were drawn largely from the medical, gynecological, obstetrical and a few from the surgical services. A majority of them required prolonged periods of bed rest for their primary diseases. All of them were considered satisfactory risks for the treatment. More recently, because of the effectiveness of this therapy, we have recommended anticoagulants for most of the patients showing no obvious con-

traindications. Most of these patients received combined heparin and Dicumarol treatment.

GROUP 2. PATIENTS TREATED WITH BILATERAL FEMORAL VEIN LIGATIONS. This group consists of patients with fairly localized thrombophlebitis with or without varicose veins, patients that were regarded as poor risks for anticoagulant therapy[8,23,51], and those who developed thrombosis and embolism soon after a major operation where the danger of serious hemorrhage was still present.

GROUP 3. PATIENTS NOT TREATED BY EITHER ANTICOAGULANTS OR VEIN LIGATION. This group consists of cases that died suddenly of massive pulmonary embolism without previous clinical evidence of venous thrombosis, a few ambulatory patients with small and localized thrombosis of the superficial veins, and a few patients in whom both types of therapy were contraindicated.

The coagulation time of the whole blood using the Lee-White modification of the Howell's method[56], and prothrombin time of the plasma by the Link-Shapiro modification of Quick's test[19,75,76] were used to control heparin and Dicumarol administration, respectively. After the initial coagulation and prothrombin studies were made, heparin in 50 mg. doses was given intravenously every 4 hours, with an initial dose of 200 to 300 mg. of Dicumarol. The subsequent daily Dicumarol dose was determined according to the prothrombin time levels. Heparin administration was discontinued as soon as the prothrombin time reached 30 or more seconds (about 20% of normal) in a specimen of blood taken at least 2 hours after the previous dose of intravenous heparin. In 4 patients, 300 mg. doses of heparin in Pitkin's menstruum were given subcutaneously with oral Dicumarol to prolong the coagulation time to about 3 times the initial readings for a period of 48 to 72 hours. An attempt was made to keep the prothrombin time between 35 and 55 seconds thereafter, using a control of from 13 to 15 seconds.

THE INCIDENCE OF THROMBOSIS AND EMBOLISM. The incidence of venous thrombosis and, or, pulmonary embolism among patients admitted to the Pennsylvania Hospital from the years 1944 through 1948 is presented graphically in Fig. 1. The sharp rise in the number of cases in 1947 and 1948 may be explained by a greater consciousness of these conditions by the medical staff. There were, however, still a number of cases not diagnosed clinically, and 13 of these died suddenly of massive pulmonary embolism. These failures are included in the untreated group as shown in Table 1. Forty of this series of 222 cases showed little or no clinical evidence of peripheral venous thrombosis and in a few of them the clinical evidence of thrombosis and embolism were overshad-

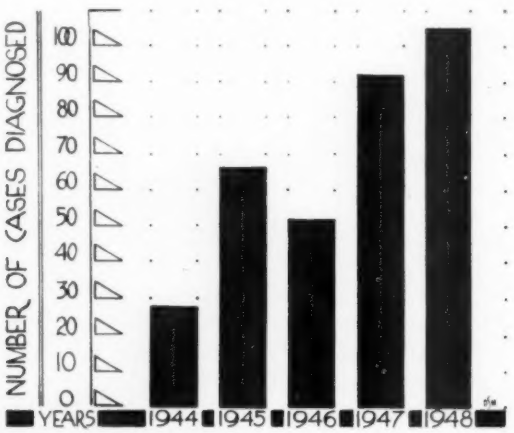


FIG. 1. The Incidence of Venous Thrombosis and, or, Pulmonary Embolism in Patients Admitted to the Pennsylvania Hospital.

TABLE 1. TYPES OF TREATMENT IN 222 CASES OF VENOUS THROMBOSIS AND, OR, PULMONARY EMBOLISM

Treatment	Cases Treated
1. Anticoagulants (Heparin and Dicumarol)	127
2. Surgical (Ligation with or without sympathetic block or sympathectomy)	47
3. Untreated:	
A. Undiagnosed	18
B. Other reasons	30
Total	222

owed by the signs and symptoms of their primary disease.

One hundred and fifty three (69%) of this series were 40 years of age or older. The distribution among the male and female sexes was 44.6 and 55.4% respectively. Forty-five per cent of the cases were medical patients and 55% of them were post-operative, post-partum or post-traumatic patients. Since this study includes a number of post-partum patients with thrombo-embolic complications, some difference in the figures between this and other reported series of cases[3,5,20,38,85] is to be expected.

SIGNS AND SYMPTOMS OF VENOUS THROMBOSIS AND PULMONARY EMBOLISM. The clinical signs and symptoms of venous thrombosis and pulmonary embolism have been described and amply discussed by a large number of observers[3,4,16,20,22,23,29, 31,38,40,42,57,60, 75,78,79]. We wish to point out that 40 of the 89 cases of pulmonary embolism in this series, and particularly those (13) who died suddenly of massive pulmonary embolism, presented few or no signs and symptoms of peripheral venous thrombosis when the accident occurred. The frequency with which the more common signs and symptoms of venous thrombosis and pulmonary embolism have been observed in this group of patients are listed in Table 2.

SOURCES OF PULMONARY EMBOLI OTHER THAN THE LOWER EXTREMITIES. It has been the general belief that nearly all pulmonary emboli have their origin in the deep veins of the lower extremities. A careful analysis of this series, however, suggests that the origin of the venous thrombi, in many of the so-called "silent" or "bland phlebothrombosis," are to be found in regions proximal to the femoral vessels. The clinical and pathological evidences for this are: 1, Postmortem examination of 4 of the fatal cases with massive pulmonary embolism, who showed patent femoral veins, revealed soft blood clots in the inferior vena cava, common iliac, iliac, hypogastric, and other veins in the pelvis. A fifth patient had multiple pulmonary emboli originating from internal jugular, subclavian, and innominate veins. 2, There were 5 patients with pulmonary emboli subsequent to bilateral femoral vein ligations. 3, Five patients developed retrograde venous thrombosis from 10 to 14 days after the episodes of pulmonary embolism had occurred. Venograms made in 2 of these patients soon after the embolization showed good visualization of the deep veins of the lower extremities. 4, Certain medical

TABLE 2. ANALYSIS OF SIGNS AND SYMPTOMS OF 222 PATIENTS WITH THROMBO-EMBOLIC DISEASES

Venous Thrombosis	Percentage Positive	Pulmonary Embolism	Percentage Positive
Tenderness, legs	67.8	Pain in the chest	65.0
Dilated superficial veins	56.3	Dyspnea	51.2
Local swelling	54.9	Pulmonary physical signs	41.2
Local pain	44.8	Hemoptysis	20.8
Dorsi-flexion sign	35.8	Shock and Collapse	15.1

and surgical conditions that are known to initiate thrombotic processes elsewhere in the body often favor the production of "primary" pulmonary embolism. These predisposing factors and the number of times they were found to be responsible for embolic complications are listed in Table 3.

ROENTGEN-RAY STUDIES. Venograms were made in 65 (about 30%) of the patients in whom thrombosis of the deep veins of the legs was suspected. The roentgenographic findings were often difficult to interpret in the light of clinical signs and symptoms. The procedure does not seem justifiable in patients where a diagnosis can be made by the clinical history and physical findings. This procedure, however, may be helpful in an occasional patient who presents certain diagnostic problems. On the basis of a limited experience, we agree with Allen, Loewe, de Takats and others that venograms are not necessary and cannot always be relied upon in the diagnosis of thrombophlebitis[3,4,22,30,57,70].

TABLE 3. CONDITIONS PREDISPOSING TO "PRIMARY" PULMONARY EMBOLISM

Predisposing Factors	Number of Cases
1. Fractures of the Pelvis and Femur	4
2. Arteriosclerotic Heart Disease with Auricular Fibrillation and, or, myocardial infarction	9
3. Prostatic and Bladder Operations	4
4. Pelvic and Abdominal Operations	17
5. Post-partum	3
6. Rheumatic Heart Disease with Auricular Fibrillation	3
Total	40

An analysis of our data shows that 42 of the 89 cases of pulmonary embolism had roentgenographic signs of pulmonary infarction, consolidation, atelectasis or pleural effusion. In a recent review of all the available roentgenograms, looking for localized areas of increased transparency which have been described by Westermark[80], 9 additional positive cases were reported by the roentgenologists. If we take into consideration the fact that 13 cases had no roentgenologic study because of sudden death and a number of others were not adequately studied in the early phase of pulmonary embolism because of the condition of the patient, we must conclude that a roentgenologic study is a valuable aid in the diagnosis of pulmonary embolism. The diagnostic wedge-shaped infarct shadows are often difficult to demonstrate[44]. For this reason, closer attention has been directed toward less specific roentgenological signs. Correlating these signs with the clinical picture, Carlotti and others[20] have found only "a small percentage of patients in whom normal lung fields were reported."

ELECTROCARDIOGRAPHIC CHANGES WITH PULMONARY EMBOLISM. Only 5 of the total 46 cases of pulmonary embolism (10.8%), in whom serial electrocardiograms were made, showed the typical acute cor pulmonale pattern as described by McGinn and White, Barnes, Durant and others[15,33,34,64]. In 7 others who showed symptoms of shock and collapse, the electrocardiogram showed a generalized lowering of the voltage and depression of the RS-T segments throughout the limb and precordial leads, which were fairly characteristic of the pattern of acute myocardial ischemia[61]. It was of interest that in all of 5 recent cases of pulmonary embolism in whom electrocardiograms were taken within a short period after the onset of symptoms, minor but definite changes other than the classical right heart strain pattern

were noted. The changes were transitory in nature and consisted of the development of an RS type of QRS complexes in the left arm "unipolar lead," a prominent Q wave in lead III, and changes in the appearance of QRS complexes in the precordial leads. The details of this electrocardiographic study are being prepared for publication. Two patients developed transient attacks of auricular fibrillation with the acute pulmonary episode which disappeared with clinical improvement of the patient.

EXPERIENCES WITH ANTICOAGULANT THERAPY. All but 3 of the 127 patients treated medically received combined heparin and Dicumarol therapy. These 3 patients were regarded as poor risks for Dicumarol therapy and were given heparin only. The details of the method of administration and the control of the prothrombin and coagulation times have been discussed in a previous communication[77]. In patients who had an initially elevated pro-thrombin time, a first dose of 200 instead of the usual 300 mg. of Dicumarol was given. There was 1 death in this group. This patient was seen early in the study and suffered from thrombosis of the subclavian, jugular, and innominate veins with multiple pulmonary emboli and severe congestive heart failure. She was in a critical state when the therapy was begun. Her prothrombin time quickly went out of control with relatively small doses of Dicumarol. Some bleeding from the respiratory and gastro-intestinal tracts probably contributed to her demise, although the primary cause of death was congestive heart failure. Another patient developed a second non-fatal pulmonary embolism during the course of continuous intravenous heparin administration. The intravenous heparin had been temporarily interrupted in order to prevent a prolonged elevation of the coagulation time at a dangerous level. It was a few hours after the interruption that the episode occurred. This patient received further doses of the heparin and recovered. The results of the various types of treatment used in this study are summarized in Table 4 and Table 5.

TABLE 4. VENOUS THROMBOSIS AND PULMONARY EMBOLISM SUMMARY OF TYPES OF TREATMENT

Type of Therapy	Total Cases	Simple Venous Thrombosis	Pulmonary Embolism with or without Peripheral Venous Thrombosis	Embolism after Therapy	Death
Anticoagulant	127	78	49	1*	1
Surgical	47	33	14	5	3**
Untreated	48	22	26		19
Total	222	133	89	6	23

* Occurred early in the course of heparin therapy.
** One patient died during spinal anesthesia.

THE PROTHROMBIN LEVEL NECESSARY FOR FULL THERAPY EFFECT. Our experience with Dicumarol therapy in various thrombo-embolic conditions convinces us that a moderate prolongation of prothrombin time (25 to 30 seconds or about 20 to 30% of normal) is often

TABLE 5. MORTALITY RATES OF PULMONARY EMBOLISM WITH VARIOUS TYPES OF THERAPY (EXCLUDING CASES OF SUDDEN DEATH)

Type of Therapy	Total Cases	Death
Anticoagulant	49	1
Surgical	14	3*
Untreated	13	6
Total	73	10

* One patient died during spinal anesthesia.

inadequate to produce the desired therapeutic effect or to prevent further embolic episodes. The clinical evidence for this belief is as follows: 1, In an early study of patients with acute coronary occlusion and myocardial occlusion receiving Dicumarol therapy, we encountered 4 instances of thrombo-embolic complications. The prothrombin times of these patients were between 25 to 32 seconds (about 20 to 30% of normal). Additional doses of Dicumarol were given to raise the prothrombin time to between 40 and 55 seconds (about 10% of normal) and no further embolization occurred. 2, Eleven of this group of medically treated patients, most of them suffering from chronic congestive heart failure with nutritional deficiency, had initial prothrombin time readings of 22 to 31 seconds (about 20 to 40% of normal). In spite of the existing hypoprothrombinemia, these patients developed venous thrombosis and pulmonary embolism. 3, Four patients with thrombophlebitis treated early in the course of the study were given inadequate doses of Dicumarol. They did not show satisfactory clinical response until the prothrombin time reached 34 or more seconds (13% of normal or less). All 4 had a prolonged convalescence with more pain and edema of the legs compared with others who received more prompt and adequate therapy. It seemed that the delay in recovery and the unsatisfactory end results were due to a continuation of a thrombotic process which might have been terminated by more adequate therapy. It is our opinion that a significant number of patients showing a tendency to intravascular thrombosis will be benefited only after the prothrombin time has been elevated and maintained with Dicumarol at 35 to 55 seconds (about 10 to 13% of normal).

Complications and Untoward Reactions with Anticoagulant Therapy. The intermittent intravenous method of administration of heparin, guided by coagulation time studies before the first and second doses, was satisfactory and safe in our hands. One patient developed a persistent elevation of temperature during the period of heparin administration. A second patient developed severe pain, local tenderness, edema and ecchymosis following one injection of 300 mg. of heparin in Pitkin's menstruum.

In spite of the fact that the prothrombin concentration of the majority of this series of patients was maintained at a relatively low level, only 6 incidences of hemorrhage were observed. Besides the fatality reported in the previous section, there were 3 patients with uterine bleeding, 1 patient with profuse bleeding from a prostatectomy wound, and 1 patient with hemarthrosis and epistaxis. These 5 patients responded well to intravenous vitamin K (72 mg.) and whole blood transfusions (500 cc. of fresh blood). It has been observed that dangerous hemorrhage rarely occurs in patients who do not have an open wound when the prothrombin time is not elevated above 60 seconds (about 5% of normal). Three patients complained of nausea and vomiting when Dicumarol was taken before meals. One patient developed spotty, erythematous, macular skin eruptions which cleared after the therapy was discontinued.

Follow-up Studies of the Treated Patients. Eighty-one (46%) of the 174 medically and surgically treated patients were followed from 1 to 21 months after their discharge from the hospital. Fifty-two (64%) of this group of patients have been symptom free and show no sign of venous insufficiency in the affected limbs. A sense of heaviness and distention with a small amount of pitting edema of the

legs was demonstrable in 26 of the 81 patients. All of these 26 patients were advised to use elastic bandages or stockings for support. Moderate to fairly severe degrees of residual venous insufficiency and lymphedema were observed in 4 patients.

Discussion. Although much attention has recently been given to the early recognition of thrombo-embolic diseases, it is apparent that this condition is still directly or indirectly responsible for a substantial number of deaths in general hospitals. Before a widespread prophylactic use of anticoagulants[8,11,12,16,67,86] can be made practical and available to post-operative, post-partum, chronically ill, debilitated, and bed-ridden patients, constant alertness and prompt treatment of suspicious cases of venous thrombosis must be practiced in order to reduce fatalities from pulmonary embolism.

Unfortunately, 40 (18%) of this series of 222 cases developed pulmonary embolism without the warning signs of peripheral thrombophlebitis, despite constant attention and inspection of the lower extremities. Thirteen of this group of 40 cases died before any treatment could be instituted. This observation is in accord with the recent autopsy finding of Dehlinger and Reimenschneider[28] and definitely suggests that a limited form of prophylactic program should be adopted for patients who, in our present knowledge, are prone to thrombo-embolic complications.

In reviewing the cases of the so called "silent" venous thrombosis with "primary" embolism, it was interesting to note that they were all patients who suffered from chronic heart disease, generalized carcinomatosis, injury and, or, operations in the abdominal and pelvic regions. In each of the patients, there was reason to believe that the site of venous thrombosis was either cardiac, abdominal or pelvic in origin. Definite pathological and clinical evidence was also presented to prove that the sources of the pulmonary emboli were proximal to the deep veins of the lower extremities. While it is true that there is a predilection of venous thrombosis for the lower extremities[1,22,44,52,63,74,85], we cannot concur with the opinion of Allen and Hampton and Castleman that as high as 95% of thrombi are located in the veins of the legs[1,44]. On the basis of our observations plus the statistics on thrombus location published by other investigators[6,21,26,27,32,36,58,62,65,81,85], we are inclined to believe that many cases of "silent" or "bland phlebothrombosis" are cases similar to those under discussion. This concept helps to explain some of the obscure sources of pulmonary embolism[45,50,85]. It may also explain the wide difference in the figures published by various observers concerning the frequency with which the leg veins were involved in various series of cases; and the not infrequent occurrence of pulmonary embolism after bilateral femoral vein interruptions[1,2,3,6,14,22,26,31,32,44,46,58,68].

The therapeutic value of heparin and Dicumarol in the treatment of thrombo-embolic diseases has been established through the accumulated studies of a large number of investigators[7,11,12,16,17,35,37,38,68,69,77,83]. Heparin by virtue of its multiple actions on the coagulating, enzymic and other systems of the blood, is indisputably superior to Dicumarol. However, the cost and difficulty in administration preclude its use in a number of patients where a prolonged anticoagulant effect is desired. The principal action of Dicumarol is to inhibit prothrombin activity[9,18] and to exert only weak inhibitory effects on other parts of the coagulating mechanism. These latter effects are detectable only by special laboratory methods[53,59,82]. Neverthe-

less, the drug has been found to be useful in the treatment of thrombosis and embolism in a large number of cases studied, when the prothrombin concentration of the blood has been reduced to 20 to 30% of normal. Although the majority of patients respond well to this moderate degree of reduction of prothrombin, further pulmonary emboli have been observed by us and others[13,24,84,86], in patients under the supposedly "full effect" of Dicumarol. Eleven of our patients developed venous thrombosis and pulmonary embolism while their initial prothrombin concentrations were from 19 to 43% of the normal. In our opinion, an elevation of prothrombin time from 35 to 55 seconds (around 10 to 13% of normal) by the Link and Shapiro modification of Quick's non-dilution method should be secured for the full therapeutic effect.

The hazards of hemorrhage and reactions in patients treated by anticoagulant therapy were carefully analyzed. The dangers were minimal and the figures obtained in this series were found to be similar to the reports of the other investigators[11,13,25,39,54,72]. The hemorrhagic complications were easy to control with vitamin K and blood transfusions, and mild drug reactions rarely interfered with the proper treatment of the patient.

Follow-up studies of 46% of the treated patients showed that the end results were very satisfactory. We wish to stress the importance of early and vigorous anticoagulant therapy in order to preserve the patency of the collateral venous and lymphatic channels, so that chronic edema and ulcers can be reduced to a minimum.

Summary. 1. A series of 222 cases of venous thrombosis with and without pulmonary embolism is presented. Of these, 127 patients were treated with heparin and Dicumarol.

2. There were 69% of the patients 40 years of age or older, and 45% of the total number were medical patients.

3. In 40 patients, there occurred few or no signs and symptoms of peripheral venous thrombosis before the onset of pulmonary embolism. Clinical and pathological evidence proved that the source of the pulmonary emboli in many of these patients was proximal to the deep veins of the legs.

4. In only 5 instances, among a total of 46 patients with pulmonary embolism in whom electrocardiographic studies were available, was an acute "cor pulmonale pattern" evident. In 5 other patients with electrocardiograms obtained within 2 hours of pulmonary embolization, an RS pattern of the QRS complexes appeared in Lead aVL and as far as the 4th and 5th precordial positions. This electrocardiographic pattern was transitory and usually disappeared within a few hours after the acute episode.

5. Despite considerable vigilance, 13 patients died suddenly from massive pulmonary embolism before treatment could be instituted. It seems rational to adopt a program of prophylactic therapy with anticoagulants in certain susceptible groups of patients.

6. Clinical evidence is presented to show that moderate reduction of prothrombin concentration with Dicumarol may be inadequate to bring about the desired therapeutic effect. In our experience, it is necessary to prolong and maintain the prothrombin time at 35 to 55 seconds (about 10 to 13% of normal prothrombin concentration) using the Link-Shapiro technique of prothrombin time determination, in order to obtain the optimum benefit in patients with thrombotic and thrombo-embolic diseases.

REFERENCES

1. **Allen, A. W.:** Bull. New York Acad. Med., **22,** 169, 1946.
2. Idem.: Surg., Gyn. and Obst., **82,** 232, 1946.
3. Idem.: Ibid., **84,** 519, 1947.
4. **Allen, A. W., Linton, R. R.,** and **Donaldson, G. A.:** Surgery, **118,** 728, 1943.
5. Idem.: J. Am. Med. Assn., **128,** 397, 1945.
6. Idem.: Ibid., **133,** 1268, 1947.
7. **Allen, E. V.:** Proc. Staff Mayo Clin., **20,** 302, 1945.
8. Idem.: J. Am. Med. Assn., **134,** 323, 1947.
9. **Allen, E. V., Barker, N. W.,** and **Waugh, J. M.:** J. Am. Med. Assn., **120,** 1009, 1942.
10. **Allen, E. V., Hines, E. A., Kvale, W. F.,** and **Barker, N. W.:** Ann. Int. Med., **29,** 371, 1947.
11. **Barker, N. W., Allen, E. V.,** and **Waugh, J. M.:** Proc. Staff Meet. Mayo Clin., **18,** 102, 1943.
12. **Barker, N .W., Cromer, E., Hurn, M.,** and **Waugh, J. M.:** Surgery, **17,** 207, 1945.
13. **Barker, N. W., Hines, E .A., Kvale, W. F.,** and **Allen, E. V.:** Am. J. Med., **3,** 634, 1947.
14. **Barker, N. W., Nygarrd, K. K., Walters, W.,** and **Priestley, J. T.:** Proc. Staff Meet. Mayo Clin., **16,** 33, 1941.
15. **Barnes, A. R.:** Proc. Staff Meet. Mayo Clin., **11,** 11, 1936.
16. **Bauer, G.:** J. Am. Med. Assn., **131,** 196, 1946.
17. **Bruzelius, S.:** Acta Clin. Scand., (Suppl. 100) **92,** 1, 1945.
18. **Butt, H. R., Allen, E. V.,** and **Bollman, J. L.:** Proc. Staff Meet. Mayo Clin., **16,** 388, 1941.
19. **Campbell, H. A., Smith, W. K., Roberts, W. L.,** and **Link, K. P.:** J. Biol. Chem., **138,** 1, 1941.
20. **Carlotti, J., Hardy, I. B., Linton, R. R.,** and **White, P. D.:** J. Am. Med. Assn., **134,** 1447, 1947.
21. **Cohn, R.,** and **Walsh, J.:** Stanford Med. Bull., **4,** 97, 1946.
22. Combined Staff Clinics of College of Physicians and Surgeons: Thrombo-embolism, Am. J. Med., **3,** 753, 1947.
23. Conference on Therapy: Treatment of Thrombophlebitis, Am. J. Med., **3,** 231, 1947.
24. **Cosgriff, S. W., Cross, R. J.,** and **Habif, D. V.:** Surg. Clin. N. Am., **28,** 324, 1948.
25. Idem.: J. Am. Med. Assn., **138,** 405, 1948.
26. **Crucher, R. R.,** and **Daniel, Jr., R. A.:** Surgery, **23,** 47, 1948
27. **Davis, A.,** and **Porter, M.:** Brit. Med. J., **1,** 718, 1944.
28. **Dehlinger, K.,** and **Riemenschneider, P.:** New England J. Med., **240,** 497, 1949.
29. **de Takats, G.,** and **Fowler, E. F.:** Surgery, **17,** 153, 1945.
30. **de Takats, G.,** and **Jesser, J. H.:** J. Am. Med. Assn., **114,** 1415, 1940.
31. **Donaldson, G. A.:** Surg. Clin. N. Am., **27,** 1037, 1947.
32. **Durant, T. M.:** Med. Clin. N. Am., **30,** 1249, 1946.
33. **Durant, T. M., Ginsberg, I. W.,** and **Roesler, H.:** Am. Heart J., **17,** 423, 1939.
34. **Durant, T. M., Long, J.,** and **Oppenheimer, M. J.:** Ibid., **33,** 269, 1947.
35. **Duryee, A. W.:** Bull. New York Acad. Med., **20,** 604, 1944.
36. **Erb, W. H.,** and **Schuman, F.,** quoted by Kirby, C. K.: Am. J. Med. Sci., **215,** 220, 1948.
37. **Evans, J. A.:** Ann. Int. Med., **17,** 970, 1942.
38. **Evans, J. A.,** and **Boller, R. J.:** New England J. Med., **236,** 392, 1947.
39. **Evans, J. A.,** and **Dee, J. F.:** Ibid., **238,** 1, 1948.
40. **Fine, J.,** and **Starr, A.:** Surgery, **17,** 232, 1945.
41. **Fleichner, F., Hampton, A. O.,** and **Castleman, B.:** Am. J. Roentgen., **46,** 610, 1941.
42. **Friedberg, C. K.,** and **Henry, H.:** J. Am. Med. Assn., **131,** 196, 1946.
43. **Frykholm, R.:** Surg., Gyn. and Obst., **71,** 307, 1940.
44. **Hampton, A. O.,** and **Castleman, B.:** Am. J. Roentgen., **43,** 305, 1940.
45. **Hampton, A. O., Prandoni, A. G.,** and **King, J. T.,** Bull. Johns Hopkins Hosp., **76,** 215, 1945.
46. **Hodges, H. H.,** and **Freeman, N. E.:** Am. J. Med. Sci., **213,** 226, 1947.
47. **Homans, J.:** Am. J. Surg., **38,** 316, 1937.
48. Idem.: Circulatory Diseases of the Extremities, New York, Macmillan Company, 1939.
49. Idem.: Am. J. Surg., **44,** 3, 1939.
50. Idem.: New England J. Med., **229,** 309, 1943.
51. Idem.: Am. J. Med., **3,** 345, 1947.

52. **Hunter, W. C., Sweeden, V. D., Robertson, T. D.,** and **Snyder, G. A. C.:** Arch. Int. Med., **68,** 1, 1941.
53. **Hurn, M., Barker, N. W.,** and **Mann, F. D.:** Variations in Prothrombin and Antithrombin Following the Administration of Dicumarol. In press.
54. **Jorpes, J. E.:** Heparin in the Treatment of Thrombosis, 2d ed., London, Oxford University Press, 1946.
55. Idem.: Ann. Int. Med., **29,** 361, 1947.
56. **Lee, R. L.,** and **White, P. D.:** Am. J. Med. Sci., **145,** 496, 1913.
57. **Loewe, L.:** Am. J. Med., **3,** 447, 1947.
58. **Loewe, L., Rosenblatt, P.,** and **Hirsch, E. J.:** J. Am. Med. Assn., **130,** 386, 1946.
59. **Maloney, W. C., Murphy, A. S.,** and **Harrington, W. J.:** Am. J. Med., **5,** 40, 1948.
60. **Marshall, D. S.:** The Recognition and Emergency Treatment of Venous Thrombosis and Its Complications. In press.
61. **Master, A. M., Dack, S.,** and **Grishman, A.:** J. Mt. Sinai Hosp., **14,** 8, 1947.
62. **Mathew, G. D.:** Edinburgh Med. J., **54,** 641, 1947.
63. **McCartney, J. S.:** Surgery, **17,** 191, 1945.
64. **McGinn, S.,** and **White, P. D.:** J. Am. Med. Assn., **104,** 1473, 1935.
65. **Moran, T. J.:** Am. J. Clin. Path., **17,** 205, 1947.
66. **Morton, J. J., Mahoney, E. B.,** and **Mider, G. B.:** Ann Surg., **125,** 590, 1947.
67. **Murray, G.:** Surg. Gyn. and Obst., **84,** 665, 1947.
68. **Murray, G. D. W.,** and **Best, C. H.:** Ann. Surg., **108,** 163, 1938.
69. **Murray, G.,** and **MacKenzie, R.:** Am. J. Surg., **57,** 414, 1942.
70. **Neuhof, H.:** J. Mt. Sinai Hosp., **14,** 110, 1947.
71. **Ochsner, A.:** Surgery, **17,** 240, 1945.
72. **Parker, R. L.,** and **Barker, N. W.:** Proc. Staff Meet. Mayo Clin., **23,** 367, 1948.
73. **Powers, J. H.:** Am. J. Med., **3,** 224, 1947.
74. **Sagall, E. L., Bornstein, J.,** and **Wolff, L.:** Arch. Int. Med., **76,** 234, 1945.
75. **Shapiro, S.:** J. Exp. Med. Surg., **2,** 103, 1944.
76. **Shapiro, S., Sherwin, B., Redish, M.** and **Campbell, H. A.:** Proc. Soc. Exp. Biol. and Med., **50,** 85, 1942.
77. **Vander Veer, J. B., Marshall II, D. S.,** and **Kuo, P. T.:** Trans. and Studies Coll. of Phys. of Phila., **16,** 67, 1948.
78. **Veal, J. R.,** and **Hussey, H. H.:** Surgery, **17,** 218, 1945.
79. **Veal, J .R., Hussey, H. H.,** and **Barnes, E.:** Surg. Gyn. and Obst., **84,** 605, 1947.
80. **Westermark, N.:** Acta Radiol., **19,** 357, 1938.
81. **White, P. D.:** Am. J. Med. Sci., **200,** 577, 1940.
82. **Wright, H. P.:** J. Path and Bact., **57,** 382, 1945.
83. **Wright, I.,** and **Prandoni, A.:** J. Am. Med. Assn., **120,** 1015, 1942.
84. **Wright, I. S., Marple, C. D.,** and **Beck, D. F.:** Am. Heart J., **36,** 801, 1949.
85. **Zahn, D. W.,** and **Peirce, C. T.:** Am. J. Med., **5,** 717, 1948.
86. **Zilliacus, H.:** Acta Med. Scand., Suppl., **171,** 1, 1946.

TWO-YEAR FOLLOW UP REPORT OF PATIENTS WITH MILIARY AND MENINGEAL TUBERCULOSIS TREATED WITH STREPTOMYCIN§

By Paul A. Bunn, M.D.
ASSOCIATE PROFESSOR OF MEDICINE, SYRACUSE UNIVERSITY COLLEGE OF MEDICINE
SYRACUSE, NEW YORK

(From the Veterans Administration)

Results of therapy with streptomycin for 100 consecutive cases of miliary and meningeal tuberculosis were reported a year ago, after 1 year of treatment[1]. At that time (June, 1948) 24 of the original 100 patients treated were living; one other had been lost from the series and was presumed to be dead. In May, 1949, 21 of the 100, including the displaced one recently relocated, are living, and the average period of post-treatment observation of the group is now 23 months (Tables 1 and 2). This report completes a 2-year follow up on the group.

The Dead. During the past year 4 patients have died and 2 others are in terminal stages of tuberculosis. Two of the 6 are in the miliary series, 2 in the group with meningitis alone, and the remaining 2 are in the series with combined miliary and meningeal tuberculosis (Table 1; compare with

TABLE 1. PRESENT STATUS OF 100 CASES OF MILIARY AND MENINGEAL TUBERCULOSIS TREATED WITH STREPTOMYCIN (2-YEAR FOLLOW UP)

(Compares with Table 3, first report[1])

Type of Disease	Total	Dead		Living	
		No.	%	No.	%
Miliary	19•	8	42	11	58
Miliary Followed by Meningitis	13•	13	100	0	0
Miliary and Meningitis Combined	25	23	92	2••	8
Meningitis	43	35	80	8•••	20
	100	79		21	

• In Table 3 of original report[1] there were 22 cases of miliary tuberculosis; 3 of these subsequently developed meningitis and have been reclassified.
•• One moribund—central nervous system relapse.
••• One moribund—pulmonary tuberculosis.

§ The following physicians generously supplied the complete data that comprise this report: Dr. D. N. Pickar, VA Hospital, Louisville, Ky.; Dr. R. H. Wichelhausen, VA Hospital, Washington, D. C.; Dr. W. S. Schwartz, VA Hospital, Oteen, N. C.; Dr. S. T. Allison, VA Hospital, Rutland Heights, Mass.; Dr. T. S. Jennings, VA Hospital, Martinsburg, W. Va.; Dr. S. Fisher, Ft. Benjamin Harrison, Ind.; Dr. P. J. Galante, VA Hospital, Whipple, Ariz.; Dr. R. A. Goodwin, Jr., VA Hospital, Nashville, Tenn.; Dr. W. E. Roye, VA Hospital, Richmond, Va.; Dr. E. Dunner, VA Hospital, Livermore, Calif.; Dr. R. A. G. Jones, VA Hospital, Kecoughtan, Va.; Dr. R. W. Hille, VA Hospital, Bath, N. Y.; Dr. Roy Woodward, VA Hospital, Batavia, N. Y.; Dr. W. G. Lewis, VA Hospital, Walla Walla, Wash.; Dr. E. P. Sauer, VA Hospital, Dayton, O.; Dr. Arnold Shamaskin, VA Hospital, Hines, Ill.; Dr. N. P. Shumway, VA Hospital, Cleveland, O.; Dr. W. B. Tucker, VA Hospital, Minneapolis, Minn.; Dr. J. D. Davis, VA Hospital, Van Nuys, Calif.; Dr. M. N. Pusin, VA Hospital, Staten Island, N. Y.; Dr. S. L. Zimmerman, VA Hospital, Columbia, S. C.; Dr. S. J. Jacobson, Cumberland, Md.; Dr. J. W. Towey, Powers, Mich.

Table 3, first report)[1]. One individual died with evidences of recrudescence of miliary tuberculosis together with progressive, advanced, pulmonary genito-urinary, and adrenal lesions. Another in the original miliary series died as a result of an unrelated necrotizing renal arteriolitis; at autopsy no active tuberculous lesions, miliary or otherwise, were found. One patient in the meningeal series died with active meningitis and encephalitis, these being relapses of a previously diagnosed and treated tuberculous meningitis. The other patient in this series is now in the terminal stages of advancing pulmonary disease but has had no return of evidences of central nervous system infection. The fifth patient, who had miliary tuberculosis followed by meningeal tuberculosis 2 years ago, developed an infectious central nervous system recidivation that proved fatal. The last individual, still living, had a serious, and so far unresponsive, recurrence of meningeal tuberculosis 14 months after termination of a first course of streptomycin given for combined miliary and meningeal tuberculosis.

Seventy-nine of 100 patients have died since the institution of the study in the spring of 1946, and 2 others are expected to die shortly. Of these 81 individuals, 76 have died, or are dying, of their miliary and, or, meningeal tuberculosis; fatal relapses of one or the other have been observed to occur as long as 2 years after an initial "complete" remission. Three patients have died and a fourth is dying of progressive, mainly pulmonary, tuberculous disease. Only 1 patient has died of non-tuberculous disease.

The time of death after institution of therapy is important in evaluating a treatment program (Table 3). The survival record would be appreciably more impressive if those patients who died within 2 weeks of commencing therapy were excluded from consideration. In the present series, 23 patients died during the first fortnight of therapy with streptomycin and the majority of these either had no response to treatment, or the response was transient and evanescent. All patients surviving this period showed distinct improvement, although it was not maintained in 56 for one reason or another[1]. In 32 patients the remission was only temporary and, despite continued therapy, relapse and death occurred in from 30 to 120 days. After the fourth month of treatment, 24 patients have died, but the number of patients succumbing during any 30-day period has decreased progressively. All of these 24 individuals had impressive clinical responses that were maintained for

TABLE 2. SUMMARY OF TREATMENT DETAILS OF 21 SURVIVORS, MILIARY AND, OR, MENINGEAL TUBERCULOSIS

Type of Disease	No. of Pts.	Survival (after end 1st treatment) Months	Duration of Treatment Days	Intrathecal Streptomycin No. of Injections	Retreatment No. of Patients
Miliary	11	19-28 av. 23.5	105-150 av. 134.5	—	0
Meningitis	8	20-27 av. 22	100-185 av. 136	45-102 av. 67	0
Miliary and Meningitis Combined	2	21-23.5 av. 22	120-165 av. 142	44-65	1*
Miliary Followed by Meningitis	0	—	—	—	—

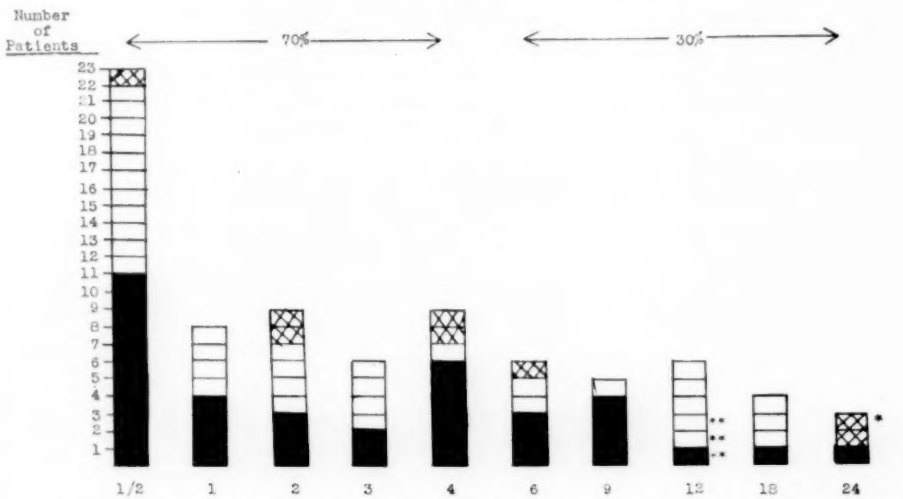
* Moribund

from 1 to 18 months after cessation of the first course of streptomycin and their recovery, during this period, was considered to be complete. There have not been sufficient studies upon the sensitivity of these patients' tubercle bacilli to describe any relationship between *in vitro* resistance to streptomycin and therapeutic response.

than 22 months. Since therapy averaged somewhat over 4 months, 18 of the 21 have lived for over 2 years from the onset of their illness and the remaining 3 for at least 23 months. (Table 2).

Active tuberculous foci, from which the original hematogenous and, or, central nervous system dissemination

TABLE 3.—MORTALITY DURING AND AFTER TREATMENT OF MENINGEAL AND MILIARY TUBERCULOSIS WITH STREPTOMYCIN



Time of death of 79 cases of miliary and, or, meningeal tuberculosis in months after institution of treatment with streptomycin.

—Meningitis alone (35 of 43).

—Miliary alone (8 of 19).

—Miliary combined with or followed by meningitis (36 of 38).

* Non-tuberculous death.
** Death from progressive tuberculous focus.

THE LIVING. The survivors deserve comment. Twenty of the 21 exhibit no evidences of active miliary or meningeal tuberculosis at the present time; one has progressive pulmonary tuberculosis.

All 21 patients have survived at least 19 months *after* the end of treatment and a majority have survived longer

presumably occurred, exist in 7 of the 21 survivors. One, in the terminal stages of pulmonary disease, has already been described. Active lesions in skin, bone, and lung exist in the remaining 6 patients; 3 of these patients have more than one active focus (Table 4). Although it is not possible to predict the eventual outcome of

any of these lesions, none of the 6 is at the moment dangerously active and it may be hoped that each will become arrested with proper therapy. Sixteen individual tuberculous foci in 14 patients have become arrested during the period of this study; 4 patients had no apparent original focus.

It seems important to examine the treatment schedule which the 21 survivors followed (Table 2). It is not obviously different from that of the patients who died. The daily intramuscular dose of streptomycin was 1.8 gm. and this amount was administered for from 100 to 185 days; in cases of meningitis, the intrathecal dose was 50 to 100 mg. injected 3 to 7 times weekly. In the present series, no patient of the 81 with meningitis survived who did not receive at least 45 separate intraspinal injections of streptomycin. As mentioned in the previous report, only 4 patients received "inadequate" intrathecal therapy; all died. It would be presumptuous to draw conclusions from these observations but, as no irreversible harm was done with intraspinal therapy, it would seem that this adjunctive route of administering streptomycin is advisable. Central nervous system and, or, cranial nerve damage is present in 18 (86%) of the 21 survivors (Table 5). Whether it is due to the disease or to its treatment cannot be stated. Although labyrinthine damage, present in 81% of the survivors, interferes to a significant degree with their existence, it has not, by itself, prevented the otherwise healthy individual's return to work.

Eleven patients (58%) have recovered from miliary tuberculosis (Table 1). Six of these individuals (31.6% of the original 19) have returned to full-time work and have become reasonably secure economically. Two others are in training programs within the Veterans Administration. Two patients are still hospitalized and one is at home in bed because of active tuberculous foci. Eight patients (20%) with apparent "cures" of tuberculous meningitis are free of evidences of central nervous system infection (Table 1). Four of these patients (9% of the original 43) are either working or are capable of doing so. Two patients are receiving therapy directed at active tuberculous foci in the lung and are still hospitalized. Two patients are incapable of working or of learning a trade because of central nervous system damage; both are blind and each is a "super vegetable." Two patients in the series with combined miliary and meningeal disease are living (8% of the original 38). One is on the point of death from a meningeal relapse. The other continues to have

TABLE 4. ACTIVITY OF TUBERCULOUS FOCI IN 21 SURVIVORS OF MILIARY AND, OR, MENINGEAL TUBERCULOSIS TREATED WITH STREPTOMYCIN

	Miliary (11)		Meningitis (8)		Miliary combined with Meningitis (2)	
Original Focus	Arr.	Act.	Arr.	Act.	Arr.	Act.
Sinus	1	1	0	0	0	0
Genito-urinary	5*	0	2	1	0	0
Bone and Joint	1	1**	0	1	0	0
Pulmonary	6	2	1	2	0	1***
None	1		2		1	

* Two had active Genito-urinary disease 1 year after first course of treatment. With retreatment, both are now arrested.

** Active Bone and Joint tuberculosis being retreated 2 years after first course of streptomycin.

*** Has received 2d course of streptomycin for active pulmonary tuberculosis.

active and advanced pulmonary tuberculosis and is totally incapacitated.

Retreatment with streptomycin for miliary and meningeal tuberculosis has not been necessary in any one of the survivors (Table 2). At least 4 have received second courses of streptomycin for persistent active foci or for prophylactic purposes during operative procedures, but in none has there been evidence of hematogenous redissemination or recurrence of central nervous system infection.

death. If this be true, antibacterial therapy will never be sufficient and some other adjunctive agent will be necessary.

2. There is a marked difference in survival rates among the 3 major forms of fatal tuberculosis included in the series. Acute disseminated miliary tuberculosis can be "cured" in somewhat over 50% of the cases (Table 2). In instances in which meningitis exists alone, about 20% survive. Few, less than 10%, of cases with combined

TABLE 5. TOXIC REACTIONS OR SEQUELAE OF DISEASE EVIDENT IN 21 SURVIVORS OF MILIARY AND, OR, MENINGEAL TUBERCULOSIS TREATED WITH STREPTOMYCIN

Toxicity	Miliary (11) Mod.	Miliary (11) Severe	Meningitis (8) Mod.	Meningitis (8) Severe	Miliary combined with Meningitis (2) Mod.	Miliary combined with Meningitis (2) Severe
Labyrinthine	4	5	4	3	0	1
Deafness	2	1	1	1	0	0
Central Nervous System Damage*	0	0	0	2	0	0
None	2		1		0	

* Blindness, dementia, paraplegia.

TABLE 6. PRESENCE OR DEVELOPMENT OF MENINGITIS IN SERIES OF 57 CASES WITH MILIARY TUBERCULOSIS

Type of Disease	Total No.	Total %	Dead No.	Dead %
Miliary Alone (no meningitis)	19	33	8	42
Miliary and Meningitis Combined	38	67		
(a) combined at start of treatment	25		23	92
(b) developed during or after treatment	13		13	100
	57	100	44	77

Summary and Conclusions. Of 100 patients with miliary and meningeal tuberculosis treated with streptomycin, 21 are living after 19 to 28 months.

In considering this series of 100 cases, 5 points bear mention: 1. Too little information has been gathered from autopsy specimens. If streptomycin is to be used more effectively, more detailed knowledge concerning causes of death is essential. It would appear that either severe encephalitis or degenerative and obstructive hydrocephalus has been the usual cause of miliary and meningeal tuberculosis will survive.

3. One danger to the survival of individuals with miliary tuberculosis is the development of meningitis. Approximately two-thirds of patients with miliary tuberculosis either have developed or will develop this complication (Table 6), and when it occurs, the chance of recovery is markedly diminished. Since it is desirable to treat meningitis as soon as possible after its development, it is recommended that diagnostic lumbar punc-

tures be performed at routine periodic intervals, in individuals being treated for miliary tuberculosis.

4. No series of cases can be safely evaluated for at least 2 years after the end of a treatment period. The success of therapeutic regimens is grossly overestimated if patients dying within 2 weeks after the start of treatment are excluded or if evaluation is made after only 6 months of observation. Survival rates in the present series of cases are almost doubled if this is done (Table 3, first report[1], Tables 1 and 3 this report).

5. A significant advance in the management of these fatal forms of tuberculosis has been accomplished. The basic ingredient in this success has been streptomycin. It is conceivable that with further manipulation of dosage schedules further gains can be expected with this drug. A more likely approach for continued advancement seems to be in the intelligent use of adjunctive materials: fibrinolysins (streptokinase), anticoagulants, accessory antibacterial agents (sulfones, para-amino-salicylic acid) and possibly other mechanical or surgical measures. It is hoped, of course, that a better and more tuberculocidal material is forthcoming.

REFERENCE

1. **Bunn, P. A.:** Am. J. Med. Sci., **216**, 286, 1948.

THE EFFECT OF DIBUTOLINE SULFATE ON INTERDIGESTIVE GASTRIC SECRETION OF PEPTIC ULCER PATIENTS

By Stanley H. Lorber, M.D.*

AND

Thomas E. Machella, M.D.

PHILADELPHIA, PENNSYLVANIA

(From the Gastrointestinal Section [Kinsey-Thomas Foundation] of the Medical Clinic, Hospital of the University of Pennsylvania)

The purpose of this communication is to report the results of a study of the effect of dibutoline† (dibutylurethane of dimethyl-ethyl-B-hydroxyethyl ammonium sulfate), an atropine-like compound, on the gastric secretion of peptic ulcer patients. The study was made in search for a drug that would effectively inhibit night secretion in such cases.

Dibutoline was synthesized by Swan and White[7-12]. They also described its action as a mydriatic and cycloplegic. A depressed action on tonus and an inhibitory effect on the contraction waves of isolated strips of smooth muscle of the rabbit and of intestinal loops of the dog were demonstrated by Featherstone and White[2]. Peterson and Peterson[5] in somewhat similar experiments concluded that the drug has a direct inhibitory action on smooth muscle as well as an atropine-like effect. They also noted a depression or inhibition of insulin-induced gastric hypermotility in man following subcutaneous injections of 0.65 to 10 mg. of the drug[6]. Cummins *et al.*[1] reported the drug to be an effective "spasmolytic" agent in a variety of clinical conditions when administered intramuscularly in doses of 5 to 10 mg. as often as every 3 to 4 hours. Marquardt and his associates[3] were able to produce partial inhibition of histamine-stimulated gastric secretion in pouch dogs with 10 mg. doses of the drug. They also administered 10 mg. doses subcutaneously to 5 ulcer patients and noted either a depression or a complete suppression of acid secretion for periods not exceeding 1 hour.

Procedure. Twenty-seven experiments were made on 22 patients, all but one of whom had a roentgenologically proven peptic ulcer. In the exception, Case 12, the presence of an ulcer was suspected because the patient complained of epigastric pain that was relieved by food or alkali; Roentgen examination revealed secondary evidence of an ulcer with tenderness and irritability of the duodenal cap, but no ulcer crater.

Under fluoroscopic observation a Levin tube (No. 16 French) was introduced into the gastric antrum of the fasting subject and the gastric residuum evacuated. With the patient in a semi-recumbent or sitting position, constant suction was applied and 10 minute samples of gastric juice were collected. He was turned frequently in order to evaculate gastric juice as completely as possible and was instructed not to swallow saliva. After initial "basal" collections over a period of 40 to 60 minutes, the drug was administered subcutaneously in doses of 10 to 60 mg. and samples of gastric juice were collected until the volume of the secretion

* Present address: Fels Research Institute, Temple University School of Medicine, Philadelphia, Pa.

† We are indebted to Merck & Co. Inc., Rahway, N. J. for generous supplies of the drug. Trade mark dibutoline changed to "dibuline."

approximated that of the basal period. The response was judged by comparing the volumes of juice aspirated during comparable time intervals. Free and total gastric acidity were determined by titration with N/50 NaOH, using Töpfer's solution and phenolphthalein as indicators.

Results. A. *Volume.* The drug, when administered subcutaneously in doses of 20 to 60 mg., produced a marked diminution in the volume of gastric secretion (Tables 1 and 2). The average decreases in volume for the 30, 40, 50 and 60 mg. doses were 76 (range 56 to 85), 77 (53 to 94), 82 (74 to 90) and 62 (35 to 84) %. Doses larger than 30 mg. were not correspondingly more effective. The effect on secretion usually occurred within 3 to 10 minutes after injection and lasted from 40 to 220 minutes. The duration of the period of partial to complete inhibition was not lengthened by doses greater than 30 mg. and averaged 122 (range 80 to 200), 89 (40 to 220), 93 (90 to 100) and 93 (60 to 110 minutes, respectively, for the 30, 40, 50 and 60 mg. doses. The drug appeared to inhibit gastric secretion completely in 18 of 27 experiments during one or more 10 minute collection periods. The longest period of apparent complete inhibition of gastric secretion was 70 minutes. Complete suppression of gastric secretion for the 30, 40, 50 and 60 mg. doses averaged 45 (range 20 to 70), 11 (0 to 40), 27 (10 to 40) and 27 (0 to 60) minutes. An example of marked inhibition of secretion is shown in Figure 1.

B. *Acidity.* The titratable gastric acidity was not consistently altered during the period of decreased volume of secretion induced by the drug (Table 1). In 14 instances the acidity was apparently decreased, in 5 apparently increased (Fig. 2), while in 8 no significant change occurred. The total output of hydrochloric acid (mg.) was decreased in all instances, mainly as a result of the decrease in volume. The apparent decrease in secretion of free hydrochloric acid following the 30, 40, 50 and 60 mg. doses averaged 77 (range 63 to 96), 74 (3 to 100), 88 (77 to 96) and 72 (16 to 100) % (Table 1).

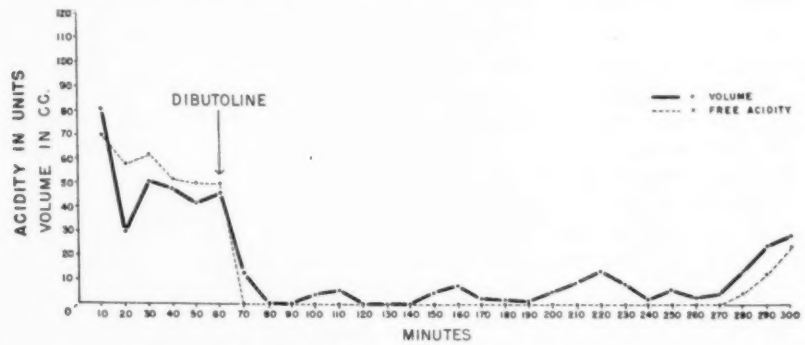


FIG. 1. Prolonged decrease in volume and free acidity of gastric secretion following a subcutaneous injection of 30 mg. of dibutoline (Case 18).

C. *Side Effects.* Mydriasis, cycloplegia and xerostomia were experienced by all subjects given the drug. Paralysis of accommodation, not always complete, usually lasted 2 to 4 hours, somewhat longer than the effect on gastric secretion. Dryness of the mouth usually occurred simultaneously with the diminution of gastric secretion. No other untoward effects were observed or complained of.

TABLE 1.—EFFECT OF DIBUTOLINE ON VOLUME AND ACIDITY OF GASTRIC SECRETION

Case No.	*Sex Age*	*Ulcer Site*	*Dose in mg.*	*Duration (in minutes) of entire period of dimin. vol. of secretion*	*Duration (in minutes) of apparent total inhibition of secretion*	*Percentage depression of gastric secretion volume*	*Percentage depression of gastric secretion mg. HCl*	*Effect on free acidity*
1	M/52	Duodenum	10	0	0	17	35	D*
2	M/58	Stomach	20	70	20	90	91	D
3	M/25	Duodenum	30	80	20	85	96	D
4	M/50	Duodenum	30	100	20	81	75	D
5	M/53	Duodenum	30	140	70	58	63	D
6	F/58	Duodenum	30	200	70	82	76	D
7	M/35	Duodenum	40	40	0	66	70	O**
8	M/43	Duodenum	40	40	40	90	82	I***
9a	M/40	Duodenum	40	50	0	79	50	I
10a	M/45	Jejunum	40	60	0	85	87	D
11	M/37	Duodenum	40	60	40	89	98	O
10b	M/45	Jejunum	40	80	0	65	49	O
12	M/55	Duodenum	40	80	0	85	100	O
13a	M/39	Duodenum	40	90	0	53	3	I
13b	M/39	Duodenum	40	90	20	62	50	I
14	M/67	Stomach	40	90	10	76	88	D
15	M/37	Duodenum	40	90	10	91	91	D
16	F/38	Duodenum	40	110	10	66	87	D
17	F/40	Duodenum	40	110	10	78	100	O
9b	M/40	Duodenum	40	120	0	69	54	O
18	M/41	Duodenum	40	220	20	94	100	D
19	M/24	Duodenum	50	90	10	83	86	O
20a	M/37	Duodenum	50	100	30	74	77	D
20b	M/37	Duodenum	50	90	40	90	96	D
21	M/42	Duodenum	60	110	0	35	16	I
22	M/45	Duodenum	60	60	20	67	100	D
9c	M/40	Duodenum	60	110	60	84	100	O

D*—decreased; O**—no effect; I***—increased

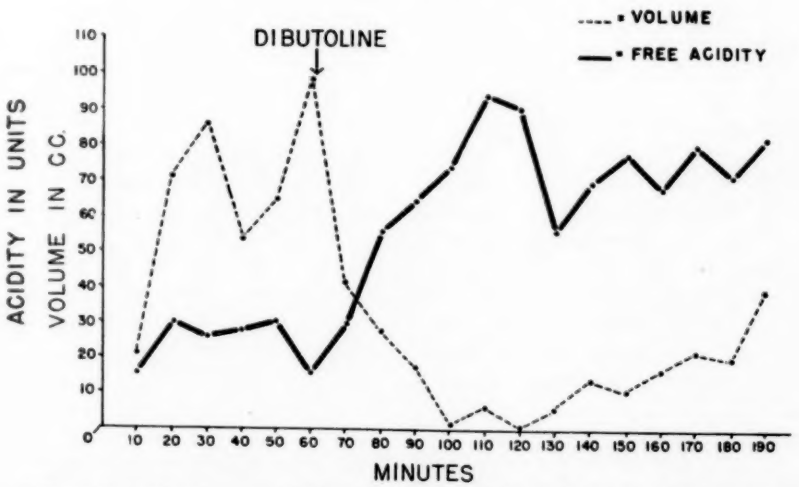


FIG. 2. Effect of a subcutaneous injection of 30 mg. of dibutoline on gastric secretion. The free acidity increased despite a diminution in volume of secretion (Case 9A).

TABLE 2.—EFFECT OF DIBUTOLINE ON VOLUME OF GASTRIC SECRETION

Minute Intervals	*Case*	1	2	4	6	5	3	10a	18	15	16	8	7	9a	9b	10b	17	13a	11	13b	12	14	19	20a	20b	21	9c	22
	−60 to −30		22*			50	69*	316	162	96	43	95	89*	178	96	225	58	76	91	65	74	110	191	88	128	88	70	34
	−30 to 0	40	34	53	53	52	69	211	136	106	27	60	121	218	89	165	51	56	48	68	44	97	100	57	150	113	46	23
	Dose in mg.	10	20	30	30	30	30	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	50	50	50	60	60	60
	0 to +30	33	6	14	16	13	20	65	14	16	15	21	56	88	43	70	9	32	16	35	12	25	39	17	19	65	8	11
	+30 to +60	18	3	23	0	29	1	12	11	2	9	17	22	9	29	61	15	30	0	16	6	25	10	21	9	62	11	11
	+60 to +90		14	31	6	0	24	187	6	31	11	41	60	31	29	88	23	12	62	12	22	32	17	12	15	43	0	20
	+90 to +120			29	7	1	46*		12	50	6			59	32		24	38		30		67	56	49	50	87	30	18
Minute Intervals	+120 to +150				5	1			15																			
	+150 to +180				5	37			25																			
	+180 to +210				9	3			14																			
	+210 to +240				28	60			66																			

* 20 minute period

D. *Comparison with Atropine.* Three of the patients given a subcutaneous injection of 2 mg. of atropine sulfate had an average diminution of secretion of 67% (Table 3). The duration of action of atropine averaged 133 minutes—approximately 35 minutes longer than that of dibutoline.

E. *Effect on Peptic Ulcer Pain.* Six patients who were experiencing ulcer pain at the time dibutoline was injected experienced complete relief in from 3 to 10 minutes. The duration of the period of relief of pain paralleled the depression of gastric secretion.

drug, if used by injection, should have a more prolonged action. It may be possible to combine the drug with some substance which will prolong its absorption and hence its action.

Our observations would tend to confirm the findings of Marquardt *et al.*[3] who compared the effects of 10 mg. of dibutoline and 1 mg. of atropine sulfate on gastric secretion. In our patients the more prolonged inhibitory action of dibutoline was probably due to the relatively larger doses used.

The side effects of dibutoline appeared to us to be less severe than those of atropine. The xerostomia was

TABLE 3.—EFFECT OF SUBCUTANEOUS INJECTION OF 2 MG. OF ATROPINE ON VOLUME AND ACIDITY OF GASTRIC SECRETION

Case No.	*Sex Age*	*Ulcer Site*	*Duration (in minutes) of entire period of dimin. vol. of secretion*	*Duration (in minutes) of apparent total inhibition of secretion*	*Percentage depression of gastric secretion volume*	*Percentage depression of gastric secretion mg. HCl*	*Effect on free acidity*
1	M/35	Duodenum	140	30	81	87	D*
2	M/41	Duodenum	140	0	76	93	D
3	M/40	Duodenum	120	30	45	34	D
Average			133	20	64	71	

* Decreased

Comment. The ability of dibutoline, in doses of 20 to 60 mg., to produce a decrease in the volume of interdigestive gastric secretion was consistently demonstrated. The decrease in volume of secretion averaged approximately 75% for an average period of 95 minutes. The inconstant effect in altering the titratable acidity of the secretion, similar to that reported for atropine[4], is not surprising in view of the fact that the inhibition of secretion is not complete. It would seem, therefore, that the relative brevity of the depressant action of dibutoline on gastric secretion would indicate that it is not the ideal drug for depressing nocturnal gastric secretion of peptic ulcer patients. Repeated injections of the drug would be necessary. The ideal

less severe and not so prolonged; we observed no central nervous system excitation despite the relatively large doses used. Atropine, however, has the distinct advantage of being effective orally while dibutoline is regarded as relatively ineffective when so administered[2].

Though dibutoline was effective in abolishing peptic ulcer pain of mild to moderate severity and the relief from pain paralleled the depression of gastric secretion, one should not conclude that the relief from pain was caused by the inhibition of gastric secretion. The ability of the drug to inhibit gastrointestinal motor activity[2,5,6] and to relax spasm is acknowledged.

Summary. 1. The effects of dibu-

toline on the interdigestive gastric secretion of 22 subjects with peptic ulcer is described.

2. Its subcutaneous administration in doses of 20 to 60 mg. produced a marked diminution in the volume of gastric secretion.

3. The duration of inhibition of secretion averaged 96 minutes for the 30 to 60 mg. doses.

4. The effect on the degree of gastric acidity was inconstant, whereas the total secretion of free hydrochloric acid was decreased in all instances.

5. Side effects encountered were xerostomia, mydriasis and cycloplegia. These were not especially troublesome except for the transient blurring of vision.

6. The comparative effects of dibutoline and atropine are discussed.

REFERENCES

1. **Cummins, G. M., Marquardt, G. H.,** and **Grossman, M. I.**: Gastroenterology, **8**, 205, 1947.
2. **Featherstone, R. M.,** and **White, N. G.**: J. Pharmacol. and Exp. Ther., **84**, 105, 1945.
3. **Marquardt, G. H., Case, J. T., Cummins, G. M., Jr.,** and **Grossman, M. I.**: Am. J. Med. Sci., **216**, 203, 1948.
4. **Mears, F. B.**: Surgery, **13**, 214, 1943.
5. **Peterson, C. G.,** and **Peterson, D. R.**: J. Pharmacol. and Exp. Ther., **84**, 236, 1945.
6. Idem: Gastroenterology, **5**, 169, 1945.
7. **Swan, K. C.,** and **White, N. G.**: Proc. Soc. Exp. Biol. and Med., **53**, 164, 1943.
8. Idem: J. Pharmacol. and Exp. Ther., **80**, 285, 1944.
9. Idem: Arch. Ophth., **31**, 289, 1944.
10. Idem: Am. J. Ophth., **27**, 933, 1944.
11. Idem: Arch. Ophth., **33**, 16, 1945.
12. Idem: Ibid., **33**, 160, 1945 (In Soc. Proc.).

CLINICAL EXPERIENCE WITH THIOMERIN*

Observations on its use in 205 Patients

By Charles D. Enselberg, M.D.
Chief of Cardiac Clinic, and Associate Visiting Physician
and
Henry G. Simmons, M.D.
Assistant Visiting Physician
New York, New York

(From the Cardiac Clinic and Medical Service, Gouverneur Hospital)

Various sulfhydryl-containing substances have been shown to diminish the toxicity of mercurial diuretics[9] without necessarily impairing their diuretic action[4]. One such combination which appears to have excellent diuretic properties is thiomerin. This is identical with mercuzanthin except that the theophylline link is replaced by sodium mercapto-acetate. The drug is readily soluble in water, and can be given subcutaneously.

The purpose of this report is to recount the clinical experience with thiomerin in 205 patients treated on the wards and in the Cardiac Clinic.

In the 11-month period from May, 1948, to April, 1949, 3314 injections totalling 5161.5 cc. of thiomerin were given. One hundred and seventy-three patients had heart disease of the common etiological types, the majority of hypertensive or arteriosclerotic origin. All had the usual systemic or

TABLE 1.—DATA ON DOSAGE IN 20 PATIENTS WHO RECEIVED 55 OR MORE DOSES OF THIOMERIN EACH.

Name	*Age*	*Diagnosis*	*No. of Doses*	*Total Dosage cc.*	*Dates*
A.D.	55	H	55	110	6/1-8/17/48
A.DiL.	66	H	75	116	8/1/48-3/31/49
H.G.	64	A	68	68	6/1/48-3/31/49
Z.K.	62	H & A	79	148	5/1/48- "
N.K.	53	R	94	114	5/48 - "
H.K.	62	A	82	154	6/48 - "
M.L.	50	H	135	214	5/48 - "
C.L.	57	H	105	204	8/48 - "
B.M.	72	H & A	55	110	5/48 - "
P.P.	80	H & A	61	61	" - "
P.Pi.	51	S	101	114	" - "
F.R.	62	H	92	92	" - "
H.R.	70	A	64	100	6/48 - "
J.R.	64	A	60	92	" - "
A.S.	61	H	57	57	5/48 -8/9/48
A.T.	68	H & A	82	101	" -3/49
J.W.	48	R	58	112	" -12/48
S.W.	55	A	63	63	7/48 -3/49
R.Y.	59	H	82	82	5/48 -3/49
H.Z.	64	A	85	159	" - "
TOTAL			1553	2271 cc.	

H—Hypertensive Heart Disease
A—Arteriosclerotic Heart Disease
R—Rheumatic Heart Disease
S—Syphilitic Heart Disease

* Thiomerin was generously supplied by Campbell Products, Inc., New York City.

pulmonary manifestations of heart failure in varying degrees. Of the 32 patients who had no heart disease, 11 had portal cirrhosis of the liver with ascites; 3, carcinomatosis with ascites; 2, chronic glomerulonephritis; 1, mesothelioma of the peritoneum; 1, postfilarial elephantiasis; and 14, miscellaneous diseases without edema. The non-edematous patients were part of the control group as described below.

The distribution according to number of injections of the drug was as follows: 55 to 135 injections, 20 patients; 25 to 50 injections, 21 patients; 10 to 24 injections, 34 patients; 3 to 9 injections, 52 patients; and 1 to 2 injections, 78 patients.

Table 1 shows the details of dosage for those who received 55 or more injections. All these patients had heart failure of moderate degree.

Method. The drug was injected subcutaneously in every case, except for 14 intravenous trials. Injections were made into the upper parts of the arms. Thiomerin was used in the same dosage and with the same frequency as the common mercurial diuretics. In the first few weeks it was given to several patients who had been under treatment with mercuhydrin, but later it was used as the sole diuretic. Management was otherwise unchanged: bed rest, digitalis, dietary restriction, and other measures being applied as indicated. No ammonium chloride or other acidifying salts were used. Weight records were obtained wherever possible, and due allowance was made for paracentesis.

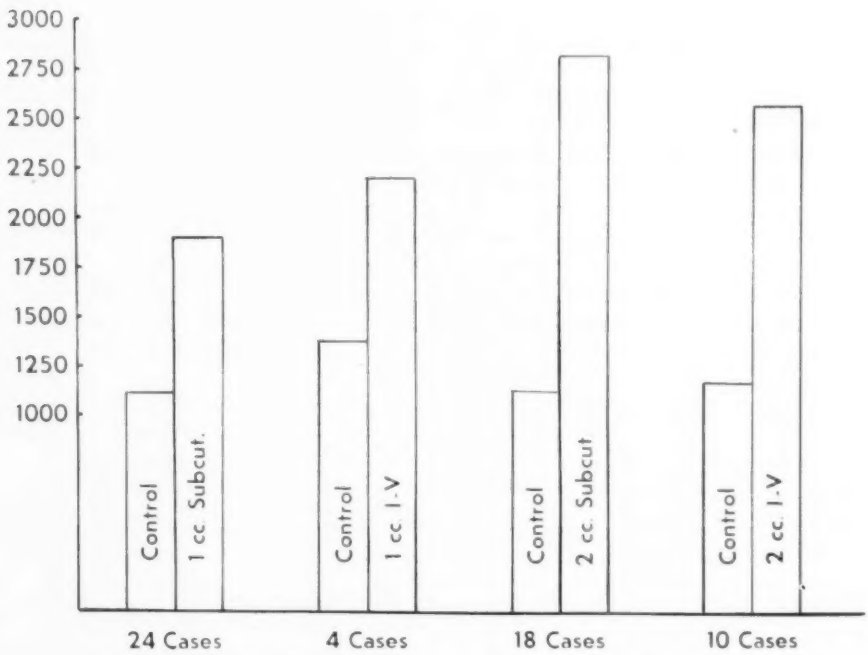


FIG. 1. Twenty-four hour output, in cc., before and after thiomerin.

Urine output measurements were made on 30 patients. Twelve of them had hypertensive and arteriosclerotic heart disease with heart failure of mild degree; 18 had no heart disease, but 3 of the latter had ascites due to cirrhosis of the liver. In each, an indwelling urethral catheter was inserted and retained for 72 hours for every trial. Urine was collected and measured at the end of each hour from 10 a.m. to 4 p.m., and at the end of the 18-hour period from 4 p.m. to 10 a.m. Control values were taken as the mean of the

first 48 hour quantities. Urine was collected for 24 hours after injection of thiomerin. Fluid intake measurements during the test periods were not made, but the output figures over the 48 hour control periods indicate that important fluctuations in intake did not occur. Onset of diuresis was judged to occur when the volume of an hourly sample sharply exceeded that of any hourly specimen in the control period. Maximal urine output was judged in the same manner.

Five patients, whose cooperation and intelligence were assured, were permitted to receive most of their injections at home. Only one administered the drug himself. The other 4 received it from members of the family.

Results. 1. URINE OUTPUT. Unequivocal diuresis occurred in all but one of the trials. The mean 24-hour outputs before and after thiomerin were as follows: Control, 1110 cc.: after 1 cc. subcutaneously, 1913 cc. (24 cases); control, 1369 cc.: after 1 cc. intravenously, 2203 cc. (4 cases); control, 1121 cc.: after 2 cc. subcutaneously, 2870 cc. (18 cases); control 1177 cc.: after 2 cc. intravenously, 2576 cc. (10 cases). These values are expressed graphically in Fig. 1.

The time of onset of diuresis varied from the end of the 1st hour to the end of the 5th hour after 1 cc. subcutaneously; from the end of the 1st to the end of the 4th hour after 2 cc. subcutaneously; and from the end of the 1st to the end of the 3rd hour after 2 cc. intravenously. The peak of diuresis followed a roughly similar distribution, but occurred about 1 hour later. These characteristics are shown graphically in Figs. 2a and 2b.

2. CLINICAL EFFECTIVENESS. The patients with congestive heart failure responded to the drug in an entirely

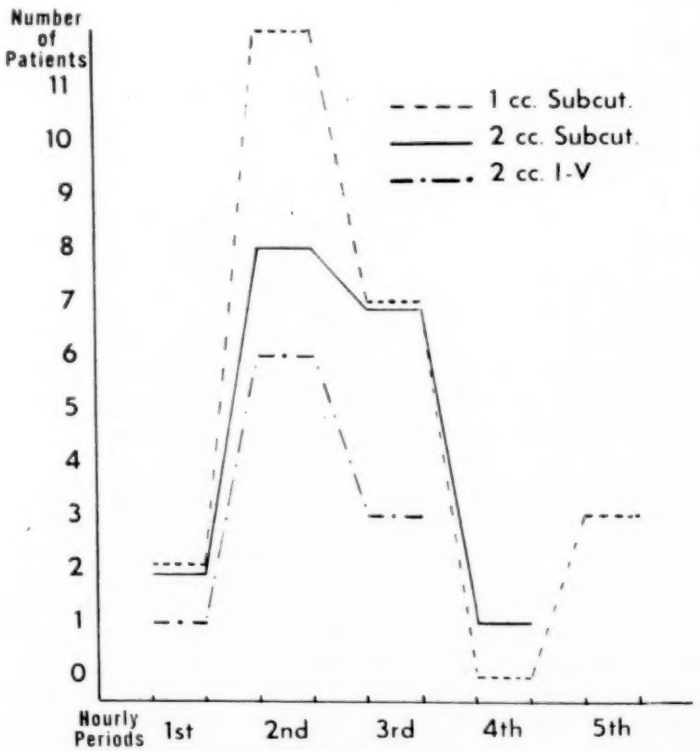


FIG. 2a. Time of onset of diuresis.

satisfactory manner. In those cases where another mercurial diuretic had been used just before thiomerin was started, the latter drug appeared to be at least as effective. In 12 cases, there was greater diuresis after thiomerin than after mercuhydrin in similar doses, but this was not taken as proof of greater efficacy of the newer drug because of the complexity of other factors such as the effect of bed rest, edema due to hepatic cirrhosis showed fair to moderate diuresis after thiomerin. One case of chronic glomerulonephritis exhibited striking diuresis. In the case of post-filarial elephantiasis, which was of 30 years' duration, thiomerin was very effective, though the edema re-accumulated rapidly.

3. Toxic Reactions. No instance of a general toxic reaction was noted, nor was there a single case of hypersensi-

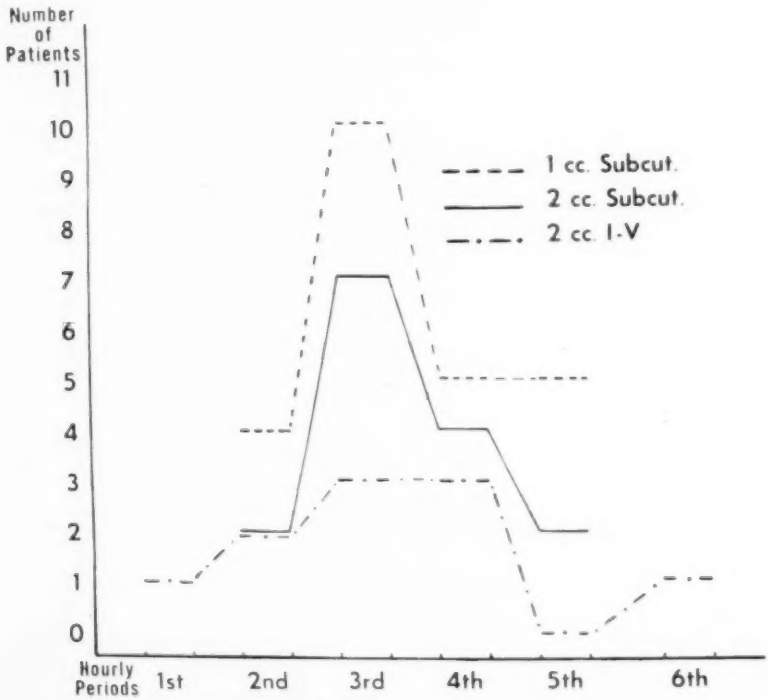


Fig. 2b. Time of occurrence of peak of diuresis.

diet, digitalization, and others. Weight curves which were typical of the great majority treated with thiomerin are shown in Fig. 3.

Five patients with intractable congestive failure, all of whom died, failed to respond to repeated injections of thiomerin. In a case of peritoneal mesothelioma there was similar failure of response.

Most of the patients with ascites and tivity of the usual type with the common allergic manifestations. Reactions attributable to excessive electrolyte or water loss did not occur or were so mild as to be missed. Spontaneous re-digitalization consequent to diuresis was not detected.

Local reactions occurred in 8 patients. These usually consisted of subcutaneous nodules, often tender, and sometimes preceded by hema-

tomas. The nodules varied in size from 3 to 20 mm. They appeared in 2 to 4 days after injection and completely disappeared within 4 weeks, except for one case where 2 nodules still remain after 5 months. Ecchymoses or hematomas not followed by nodules were observed in a few cases. The local reaction was severe in only one case, C. K., a 49-year old woman with rheumatic heart disease. After her 16th injection of 2 cc. of thiomerin, an ecchymosis appeared in the right deltoid region. This became indurated and sloughed in 9 days, leaving a clean ulcer about 1.5 cm. across which healed well. Subsequent to the appearance of the ecchymosis, she received 3 more injections in the next 8 days without untoward event. It was considered probable that her reaction was due to inadvertent intracutaneous administration or possibly to secondary infection.

Six of the 8 patients with local reactions were obese women, with considerable adiposity of the arms. In one case, after a nodule had developed in each arm, 1 injection was made into the subcutaneous tissue of the dorsum of the hand with no subsequent local reaction.

It is of interest that the nodules appeared during the first 6 months of this study. None has been noted since

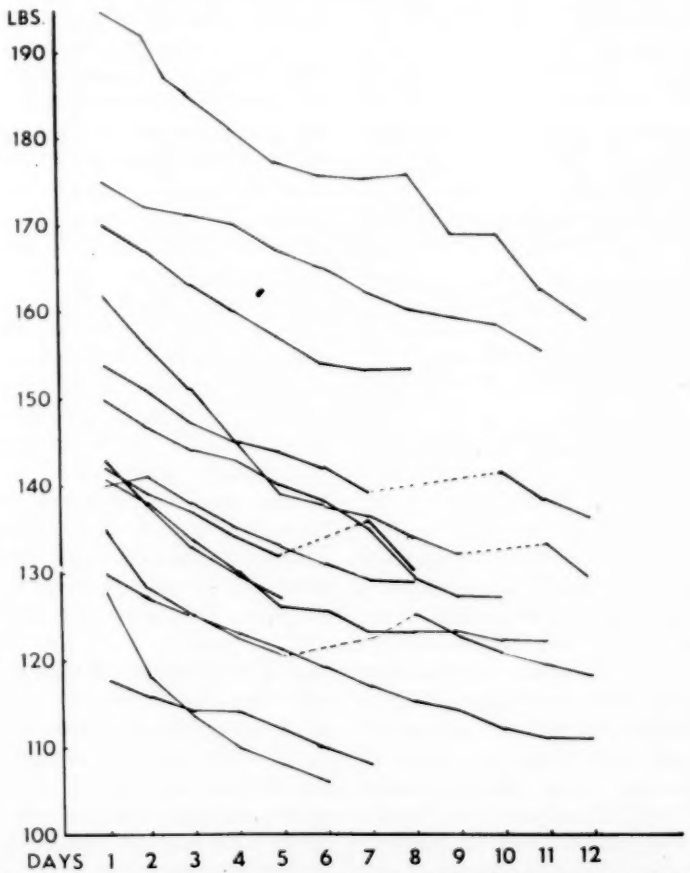


FIG. 3. Weight curves of 14 patients receiving thiomerin daily. The dotted lines represent days when no thiomerin was given.

November, 1948. Incidentally, in none of the 5 patients who received most of their thiomerin at home did any local reaction occur. These patients received almost 300 injections in their homes.

Autopsies were obtained on 5 patients who had received 3 or more doses of thiomerin. Two had received 3 injections; one, 4; one, 13; and one, 18. In no instance was there any gross or microscopic evidence suggestive of mercurial poisoning. Tubular lesions were found in one case:

Case Report. CASE 1. A. L., white male, age 60, was admitted September 28, 1948, because of edema of the legs, hands and face. There was a history of polyuria and nocturia for 3 weeks, and an episode of gross hematuria 3 days before admission followed by rapidly developing edema. Moderate systolic and diastolic hypertension, marked proteinuria and cylindruria, and moderate azotemia were present on admission. He became progressively worse, with increasing edema, uremia, and the appearance of congestive heart failure. He received 4 injections of 2 cc. each of thiomerin in the 2nd and 3rd week. On the 27th hospital day, he developed acute pulmonary edema, and died the next day.

Autopsy findings were as follows: Left ventricular hypertrophy and dilatation, right ventricular dilatation, pulmonary edema and congestion, bilateral hydrothorax, and advanced congestive changes in the liver spleen, and other organs. The kidneys were enlarged, weighing 220 and 250 gm. They were pale and edematous. Microscopically they showed lesions of acute and subacute glomerulonephritis and nephrosis. No chemical analysis for mercury was made.

Discussion. Our results indicate that the diuresis produced by thiomerin resembles that produced by the commonly used mercurial diuretics. The onset of diuresis after intravenous mercuhydrin, mercuzanthin or salyrgan-theophylline occurs in about 30 minutes, and the peak in about 4 hours[3]. Diuresis after intramuscular administration starts about 1 to 2 hours later than intravenous, and the peak is similarly later[5,10]. The response to intravenous thiomerin parallels intravenous administration of the common mercurial diuretics, and subcutaneous thiomerin parallels intramuscular injection of the common mercurial diuretics. The degree of diuresis with the older preparations depends more on the size of the dose than on the mode of administration, and this same relationship holds for thiomerin. The difference in urine output between 2 cc. of thiomerin subcutaneously and intravenously is not important, but the difference between 1 cc. and 2 cc. is striking. More precise methods of investigation[6] show that thiomerin and mercuzanthin have approximately the same qualitative and quantitative effects on the excretion of water, sodium, chloride, uric acid, mannitol, and para-amino-hippuric acid.

No attempt was made to compare the diuretic potency of thiomerin with the other mercurial preparations, but there can be little doubt that it is at least as potent, judging from clinical results. In no case did another mercurial diuretic succeed where thiomerin failed.

Experience with this new drug is too small to be certain that general toxic effects will be less frequent than with the commonly used mercurials. The latter, even by the intramuscular route, have been implicated in nephrotoxic reactions[1,11]. Since thiomerin intravenously has been shown to possess only a small fraction of the cardiac toxicity of the other preparations[7], it is to be expected that the incidence of general toxic reactions will be less. In our case of nephritis and nephrosis there is surely no indication that death was due to thiomerin. It is conceivable that the tubular lesions may have been aggravated by the mercurial. Indeed, the drug was given despite the usual strictures against the use of mercurials in acute nephritis.

Skin sensitivity has been reported[2] after the use of the common mercurials. It is of interest that no skin rash or itch appeared in any of the 205 patients who received thiomerin.

The local reactions, hematomas and nodules, resemble those often encountered after intramuscular injection of mercurial diuretics. However, the deep nodules seen after intramuscular administration of the common mercurials last longer and are more apt to be painful. One reason for this may be that the injections are generally made in the buttocks, which may be edematous in advanced congestive failure. Gross and microscopic examination of the tissues of mice has shown that thiomerin is less toxic locally than mercuhydrin or mercuzanthin[8]. The two latter drugs cause necrosis subcutaneously, and severe cellular inflammatory response intramuscularly. Thiomerin causes no gross pathological change subcutaneously, and a mild reversible inflammatory reaction intramuscularly.

Of our 8 cases with local reactions, the nodules disappeared completely in 7 within 4 weeks. In the case where a slough developed, it could well have been due to intracutaneous injection or infection. For this reason, care should be taken to inject deeply into the subcutaneous tissue. It is also possible that some of the nodules may have been due to faulty absorption from adipose tissue. If this should be substantiated by further observation, some reactions might be obviated by more careful selection of the site of administration.

It has already been mentioned that no local reactions occurred after the autumn of 1948. Information from the manufacturer reveals that the earlier batches of the drug contained 2.5 to 3% moisture, which resulted in a tendency for the powder to decompose on standing at room temperature. Subsequently this was corrected, and the currently made product has less moisture content and more stability.

The ultimate benefit of a safe and efficient mercurial diuretic which can be given by subcutaneous injection is obvious. The patient or a member of his family can administer the drug with a considerable saving of expense and physical effort on the part of the patient. Although this system was applied by only 5 of our patients, the total number of injections they received was large enough to suggest that the procedure is safe. In fact, the patient who received the greatest dosage of thiomerin, 135 injections totalling 214 cc., got 130 injections at home.

Summary and Conclusions. 1. There were given 3314 injections of thiomerin, containing 5161.5 cc., to 205 patients. Of these, 20 received 55 or more injections, and 3 received more than 100 injections each. All but 14 injections were subcutaneous.

2. Diuretic response to the drug was the same qualitatively, and appeared to be about the same quantitatively, as to the theophylline-containing mercurials.

3. No hypersensitivity reaction was encountered.

4. No instance of general toxic effect occurred.

5. Local reactions occurred in 8 patients, one of whom developed a slough. In the latter case, the reaction was attributed to faulty technique of injection.

6. No local reactions have occurred since November, 1948, presumably due to improvement in manufacturing methods.

7. Thiomerin, administered subcutaneously, is a safe and efficient diuretic. If further observation warrants it, the ultimate value of this drug may soon be realized; that is, administration in the home by a member of the family or by the patient himself.

REFERENCES

1. **Bruno, M. S.**: New Eng. J. Med., **239**, 769, 1948.
2. **Burrows, A.**, and **Stokes, W.**: Brit. Heart J., **7**, 161, 1945.
3. **De Graff, A. C.**: J. Am. Med. Assn., **136**, 1025, 1948.
4. **Farah, A.**, and **Maresh, G.**: J. Pharm. and Exp. Ther., **92**, 73, 1948.
5. **Goodman, L.**, and **Gilman, A.**: The Pharmacological Basis of Therapeutics, New York, Macmillan, 1941.
6. **Grossman, J., Weston, R. E., Edelman, I. S.**, and **Leiter, L.**: Studies on Thiomerin—A New Subcutaneously Administerable Mercurial Diuretic. In Press.
7. **Lehman, R. A.**: Proc. Soc. Exp. Biol. and Med., **64**, 428, 1947.
8. **Lehman, R. A., Taube, H.**, and **King, E. E.**: A Comparative Study of the Local Toxic Action of Mercurial Diuretics. In Press.
9. **Long, W. K.**, and **Farah, A.**: J. Pharm. and Exp. Ther., **88**, 388, 1946.
10. **Sollman, T.**: A Manual of Pharmacology, Philadelphia, W. B. Saunders, 1948.
11. **Waife, S. O.**, and **Pratt, P. T.**: Arch. Int. Med., **78**, 42, 1946.

USE OF HYALURONIDASE IN PREVENTING THE PAIN OF SUBCUTANEOUS HEPARIN INJECTION*

By M. S. Tuchman, M.D.
MEDICAL RESIDENT
AND
S. E. Moolten, M.D.
DIRECTOR OF LABORATORY
NEW BRUNSWICK, NEW JERSEY

(From the Research Division, Laboratory Service, St. Peter's General Hospital)

Certain practical difficulties in current methods of administering heparin have tended to restrict its use to that of an adjuvant to Dicumarol, generally for a few days only, in cases deemed urgently in need of anticoagulant therapy. When administered intravenously in intermittent dosage at 3 or 4 hour intervals[3] for several days heparin results not infrequently in painful phlebitis at the site of repeated introduction or in painful hematomas at such sites because of accidental leakage or oozing from the venipuncture after withdrawal of the needle. Continuous venoclysis of heparin in 5% dextrose, physiologic saline, or Ringer's solution[11,12], while reducing the number of venipunctures, adds greatly to the general discomfort of the patient and to the problems of the nursing staff. Depot injections intramuscularly of mixtures of heparin, vasconstrictor drugs and a gelatin-dextrose vehicle have shown great promise as a means of insuring continous slow absorption when given at intervals of 12 to 48 hours[4,8,9]. A theoretical drawback to this type of heparin mixture is the difficulty of controlling its effect, once given, except by supplementary administration of protamine or application of ice.

Intermittent subcutaneous injections have tended, in our experience, to produce persistent localized pain, ecchymosis, and induration, even in doses of 10 to 20 mg., contrary to the reports of others[1,2,14]. However, the subcutaneous method possesses an important practical advantage in the fact that administration of heparin can be relegated to ordinary nursing personnel.

Hechter's[6] reported success in facilitating subcutaneous infusions of saline or dextrose solution by preliminary local infiltration with solutions of hyaluronidase suggested to us the possibility that a similar effect might be obtained in the case of heparin whereby local pain and hematoma would be minimized. Hyaluronidase, an enzyme prepared from bull and ram testes and other sources, is capable of hydrolysing hyaluronic acid, a mucopolysaccharide constituting the intercellular ground substance of connective tissue and umbilical cord, and contained in synovial fluid and the vitreous humor. Hyaluronidase markedly increases the permeability of connective tissue to dyes, toxins, bacteria, and india ink[5]. In the dosages employed clinically and proved effective by Hechter[6], hyaluronidase has been shown to be devoid of harmful effect, being non-antigenic and non-toxic on

* Aided by a grant from the Shelter Rock Foundation, Inc.

repeated injection except for a nonspecific transient foreign protein reaction. He obtained direct evidence that hyaluronidase prevents pain due to distention produced by fluid administration into the tissues; that is, intradermally.

Materials and Procedures. Initially, hyaluronidase powder* was dissolved in the proportion of 1 mg. of dried material to 100 ml. of sterile physiologic saline and sterilized by passage through a Seitz filter. A fresh solution was prepared for each patient daily and kept in the refrigerator. In subsequent studies sterile material supplied in ampoules** was dissolved directly in the saline.

Heparin solution (Liquaemin-Roche), containing 10 mg. per ml., was given subcutaneously every 4 hours in dosages ranging from 25 to 100 mg., depending upon the coagulation time tested immediately before injection. The latter was determined by the nurse, employing the capillary tube method (tubes 2 mm. in diameter) in blood obtained from skin puncture. A coagulation time of about 5 minutes was regarded as normal and 15 to 30 minutes an adequate therapeutic prolongation by this method. The effectiveness of heparin in reducing platelet adhesiveness was also determined at suitable intervals by a standardized technique[10].

In preliminary experiments a site was outlined with skin pencil over the lateral aspect of a patient's upper arm or thigh. The area was infiltrated subcutaneously with 10 ml. of the hyaluronidase solution. Heparin injections (25 to 50 mg.) were given successively at intervals of 4 hours into the same site. The limiting period of satisfactory hyaluronidase effect was found to be 12 to 14 hours, following which subsequent injections into the same site caused severe pain which persisted for several hours. In later experiments 5 ml. of hyaluronidase solution (0.5 to 1.0 units per ml.) were given before each heparin injection and a fresh site was generally used for each. It was possible to give heparin with practically no discomfort to the patient if the preliminary injection of hyaluronidase was made slowly without undue pressure on the plunger of the syringe, and by use of a No. 23 or No. 24 gauge needle inserted rather deeply into the subcutanea. The needle was left *in situ* and the syringe which had contained the hyaluronidase was removed and replaced by one containing heparin solution. Heparin was delivered slowly into the prepared area, about 3 minutes being consumed for its injection. A site previously utilized was at times satisfactorily employed for reinjection of heparin 2 or 3 times in succession within a period of 12 hours without additional hyaluronidase. Although at first hyaluronidase solution was freshly prepared each 24 hours, in later studies the effectiveness of solutions kept 2 or even 3 days in the refrigerator was often found undiminished.

In all patients, preliminary control tests were made with subcutaneous injections of 10 to 15 mg. of heparin without preliminary hyaluronidase injection.

Results. Trial injection of heparin solution subcutaneously in doses ranging from 10 to 15 mg. produced moderate to severe pain at the injection site which persisted hours or days afterward. In the same patients injections of heparin in doses up to 100 mg. (10 ml.), preceded by preparatory injection of hyaluronidase subcutaneously, were strikingly successful in avoidance of pain or other complication (Table 1). In the majority of cases the effect on coagulation time and on platelet adhesiveness was as readily obtained and as consistently maintained by this means as with intravenous heparin. In the 3 cases represented in Fig. 1, heparin-hyaluronidase was administered by the subcutaneous route every 4 hours for periods of 24 hours (Cases 1, 2) to 84 hours (Case 3). Each of these patients had previously received heparin intravenously. Comparison of the coagulation time curves of the two methods of administration in these cases revealed a high degree of similarity, which suggests a rapid rate of absorption of the drug from its site of introduction.

* Obtained from Dr. E. Schwenk, Director of the Chemical Research Division of the Schering Corporation, Bloomfield, N. J. This hyaluronidase preparation contained 50 turbidity-reducing units per mg.

** Obtained from Dr. H. O. Singher, of the Ortho Research Foundation, Raritan, N. J. This hyaluronidase preparation contained 150 turbidity-reducing units per mg.

TABLE 1.—COMPARATIVE RESULTS OF HEPARIN ADMINISTERED INTRAVENOUSLY AND SUBCUTANEOUSLY WITH AND WITHOUT PRELIMINARY HYALURONIDASE INFILTRATION.

Cases	*Mode and number of heparin doses*	*Size of doses (mg.)*	*Total dosage (mg.)*	*Duration (in hours) of Effect of Heparin on Coagulation Time*			*Remarks*
				No change in Coag. Time	*Coag. Time 6-14 min.*	*Coag. Time 15-30 min.*	
1. Acute coronary occlusion, male 64	intravenous (x 7)	50–150	700	50	24		pain, mild thrombosis of antecubital veins.
	subcutaneous (x 2)	10	20	8			severe pain 2 hr.; hematoma.
	subcutaneous after hyaluronidase (0.1 mg) (x 11)	50	550		19	5	no pain or hematoma.
2. Thrombophlebitis, left leg, female 57	intravenous (x 10)	100	1000	6	9	33	moderate pain and thrombosis of antecubital veins.
	subcutaneous (x 1)	10	10	4			severe pain 4 hrs.
	subcutaneous after hyaluronidase (0.1 mg) (x 18) (× 18)	50–150	1450	1	8	15	no pain; slight hemtoma when injected too rapidly.
3. Acute coronary occlusion, female 75	intravenous	50–150	2450	3	12	45	discontinued because of severe pain and thrombosis of antecubital veins; hemaatoma.
	subcutaneous (x 1)	15	15	4			moderate pain 1½ hrs.; hematoma.
	subcutaneous after hyaluronidase (0.05-0.1 mg) (x 27)	50–150	2120	4	41	69	no pain or hematoma.

TABLE 2.—PAIN RESPONSE TO SUBCUTANEOUS INJECTION OF HEPARIN

A. PRELIMINARY INFILTRATION WITH HYALURONIDASE (0.75 TURBIDITY-REDUCING UNITS IN 5 ML. SALINE) FOLLOWED BY 30 MG. HEPARIN.

Subjective pain response	*males*	*females*	*Total no. patients*
None	5	3	8
Mild	0	2	2
Moderate	0	0	0
Severe	0	0	0

B. CONTROLS INJECTED DIRECTLY WITH 20 MG. HEPARIN.

Subjective pain response	*males*	*females*	*Total no. patients*
None	1	0	1
Mild	2	0	2
Moderate	1	2	3
Severe	2	2	4

In a subsequent study 10 patients were tested for pain responses to 30 mg. of heparin injected subcutaneously following skin preparation with hyaluronidase. As controls, 10 other patients were injected with 20 mg. of heparin directly. The results (Table 2) indicate the relative painlessness of heparin when its subcutaneous injection is preceded by hyaluronidase.

According to the results obtained thus far in 12 patients, the intermittent subcutaneous injection of hyaluronidase-heparin, if properly spaced and properly administered, appears to offer rapid and maximal dosage effect under maximal control, with a minimum of discomfort to the patient. It has proved simple enough to be developed into a routine nursing procedure. It has been found equally well adapted to the intramuscular route of administration. Its efficacy with relatively large doses of heparin in the concentration commonly employed (10 mg. per ml.), permitting subcutaneous or intramuscular injections of as much as 10 ml. (and in a few instances 15 ml.) at one time, indicate the likelihood that the method will lend itself ideally to the subcutaneous injection of even larger doses in more concentrated form (100 mg. per ml.) as now employed intramuscularly by Stats and Neuhof[13]. Recent trials of heparin in concentration of 50 mg. per ml. ("Liquaemin," High Potency, "Organon") have thus far given results essentially the same as

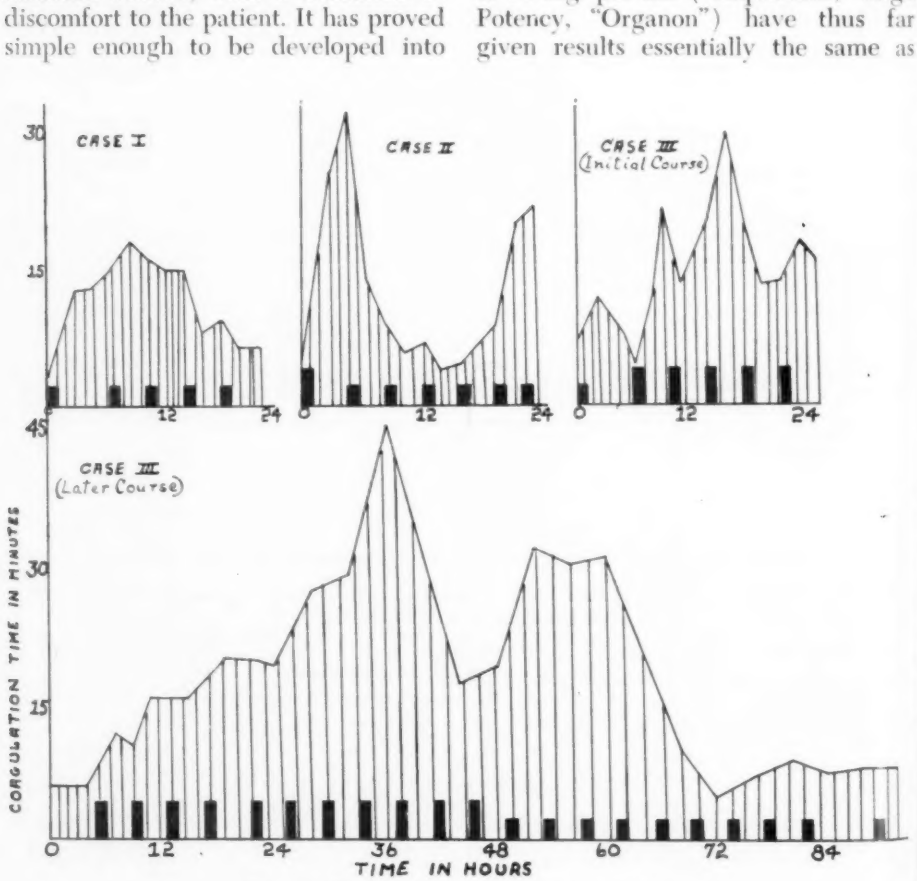


FIG. 1.—Effects of heparin on coagulation time.

Key: ▮ 50 mg. heparin. ▮ 100 mg. heparin.

with heparin in more dilute solution.

A by-product of these studies, which suggests possibly various similar clinical applications, was provided as an incidental finding in one of the patients, a woman of 75 years with a recurrent attack of coronary thrombosis. Previously this patient had received several injections of heparin into the veins of the right antecubital fossa, following which she developed venous thrombosis and infiltration of the surrounding subcutaneous tissue with a large hematoma, about 8 cm.^{2}, associated with considerable local pain. Hyaluronidase (0.03 mg. in saline) was infiltrated into the center of this area. Within 30 minutes she had virtually complete relief of pain, and in less than 3 hours almost the entire hematoma became absorbed except for a narrow marginal outline.

Summary. The repeated subcutaneous administration of heparin in doses up to 100 mg. can be given with little or no pain to the patient and with rapid effect upon the coagulation time if the site of injection is first infiltrated with a small amount of hyaluronidase solution. The absorption rate and coagulation time curves are almost identical with those produced by intermittent intravenous injections of heparin at the same intervals and in similar dosage. The procedure is relatively simple and easily carried out by the nursing staff. Hyaluronidase infiltration was found effective in 1 case in aiding in rapid resorption of a large painful hematoma.

REFERENCES

1. **Cosgriff, W.**: Presented at 23rd Clin. Congr. of Am. Coll. of Surgeons, New York, Sept. 7, 1947.
2. **Cosgriff, W., Cross, R. J.**, and **Habif, D. V.**: Surg. Clin. No. Am., **28,** 324, 1948.
3. **Crafoord, C.**, and **Jorpes, E.**: J. Am. Med. Assn., **116,** 2831, 1941.
4. **De Takats, G.**, and **Rogers, E. M.**: J. Lab. and Clin. Med., **33,** 1652, 1948.
5. **Duran-Reynals, F.**: Bacteriol. Rev., **6,** 197, 1942.
6. **Hechter, O., Dopkeen, S. K.**, and **Yudell, M. H.**: J. Pediat., **30,** 645, 1947.
7. **Jorpes, J. E.**: Heparin in the Treatment of Thrombosis, London, Oxford University Press, 1946.
8. **Loewe, L.**, and **Hirsch, E.**: J .Am. Med. Assn., **133,** 1263, 1947.
9. **Loewe, L., Rosenblatt, P.**, and **Hirsch, E.**: Ibid., **130,** 386, 1946.
10. **Moolten, S. E.**, and **Vroman, L.**: Am. J. Clin. Path., **19,** 701, 1949.
11. **Murray, D. W. G.**, and **Best, C. H.**: J. Am. Med. Assn., **110,** 118, 1938.
12. **Murray, D. W. G., Jaques, L. B., Perrett, T. S.**, and **Best, C. H.**: Surgery, **2,** 163, 1937.
13. **Stats, D.**, and **Neuhof, H.**: Am. J. Med. Sci., **214,** 159, 1947.
14. **Walker, J.**: Surgery, **17,** 54, 1945.

THE ETIOLOGY OF PULMONARY ARTERIOLOSCLEROSIS (AYERZA'S SYNDROME)

WITH REPORT OF AN ILLUSTRATIVE CASE

By Simon S. Leopold, M.D.
ASSOCIATE PROFESSOR OF CLINICAL MEDICINE
UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PENNSYLVANIA

(From the Medical Division of the Hospital of the University of Pennsylvania)

In 1901, Abel Ayerza in an unpublished clinical lecture at the National University of Buenos Aires, described a cardiac patient with intense cyanosis *(Cardiacos negros)* who at necropsy showed hypertrophy and dilatation of the right auricle and right ventricle, and the microscopic evidences of chronic infection of the bronchi. Neither the gross nor the microscopic appearance of the pulmonary vessels was described. In 1905, Escudero[8] in a necropsy report of a similar case, found atherosclerosis of the pulmonary artery and its larger branches. In 1909, Marty[10] called this condition "Ayerza's disease". In 1912, Arrillaga[2] reported 11 cases, including Ayerza's original one.

In Arrillaga's words, translated freely from the Spanish:

"There is nothing in the course of chronic bronchitis or emphysema that foretells the later onset of Ayerza's disease. However, one may surmise the probable occurrence of the latter, if there exists a low-grade infection, syphilis, malaria, or general toxic states. The story is as follows: A patient suffers from chronic bronchitis and, or, emphysema. For 20 or more years, there is constant cough with free expectoration of mucus or mucopurulent material. Gradually and insidiously there takes place a change in the clinical picture. There appears cyanosis, most marked in the face, followed in a few months by dyspnea on effort. The latter increases in severity until the patient is confined to bed. Cyanosis and dyspnea are the only manifestations of cardiac weakness. One does not see the other evidences of 'right-sided failure', such as fullness of veins of neck, enlarged and tender liver, edema of the lower extremities, and pulmonary basal congestion. This serves to differentiate Ayerza's disease from chronic *cor pulmonale*. The cyanosis is not affected by rest in bed, and it is so marked and characteristic that it has led to the designation of this disease as 'black cardiacs'. The cyanosis involves the whole face down to the middle of the neck, and includes the oral and ocular mucosa as well as the hands and feet. Clubbing is present. The cyanosis is worse during sleep, the patient actually appearing to be black in color. There is likewise a lowered surface temperature and the patient complains about his cold extremities. Similarly there is polycythemia, but no abnormal cells are seen in the peripheral blood. The next important sign is dyspnea, which is very marked and in the advanced case exists even while the patient is at absolute rest in bed. Cough and expectoration persist. The 'black cardiac' is a rather young patient around 40 years of age, with a long-standing history of chronic bronchitis and repeated attacks of pneumonia, which goes back 8 to 20 years. Bronchial asthma is common. This persistent bronchopulmonary disease culminates in the loss of alveolar elastic tissue with its production of pulmonary emphysema. Ordinarily one would expect the occurrence of chronic *cor pulmonale* and early right-sided cardiac failure as it occurs in cases of mitral valvular disease (stenosis), chronic pulmonary fibrosis, and asthma. However, these cases of Ayerza's behave differently. Marked right

ventricular hypertrophy occurs early and failure develops late—not early—and is the result of increased pressure in the lesser circulation that develops secondary to pulmonary sclerosis. The pathologic findings include those of chronic bronchopulmonary disease, pulmonary emphysema, marked right ventricular hypertrophy, and marked changes in the pulmonary arteries, analogous to those seen in the vessels of the greater circulation in systemic hypertension. There occur marked intimal thickening with atheroma formation, loss of elastic fibers with connective tissue proliferation, especially in the inner half of the media; narrowing of the vascular bed, with sclerosis as the end result. The first portion of the pulmonary artery and its two main branches are dilated, but smooth. They escape the atherosclerotic process. The latter starts at the hilus and becomes more pronounced in the intrapulmonary portions of the artery, affecting principally the finer branches."

In order to obtain information concerning the actual incidence of pulmonary arteriosclerosis, Brenner[7] studied the large and small pulmonary vessels in 100 consecutive, unselected autopsies, and found that some degree of pulmonary arteriosclerosis was present in 97. In 3 children, all under 10 years of age, there was none. He concluded that "sclerosis of the small muscular arteries is almost constant in people over 40, irrespective of the presence or absence of cardiac or chronic pulmonary disease, but its frequency in those under 40 and its severity in those over 40 are somewhat increased in the presence of chronic cardiac or pulmonary disease."

Etiology. In a discussion of the etiology of secondary pulmonary arteriosclerosis, Brenner[7] states that the effect of pulmonary emphysema on the obstruction of blood flow through the lungs is doubtful because of the great reserve of pulmonary capillaries. In substantiation of this opinion, he cites Alexander[1], who studied 50 patients with long-standing asthma and emphysema and found electrocardiographic evidences of right ventricular preponderance in only 3. One of these also had mitral stenosis. Brenner concludes that only in extremely advanced cases of pulmonary disease is the pulmonary circulation likely to be obstructed. In regard to cardiac disease as an etiologic factor, he believes that it *per se* does not influence the frequency and severity of pulmonary vascular sclerosis, but if congestive failure is present, the frequency and severity of arteriosclerosis are increased in all parts of the pulmonary vascular bed.

There is no evidence that systemic hypertension is a factor in the production of pulmonary arteriosclerosis.

In regard to primary pulmonary arteriosclerosis, there is unanimity of opinion that it is rare. Moschcowitz[11] expressed his disbelief in its existence, MacCallum[9] accepted 1 case in 12,000 necropsies, and Brenner[7] discarded all but 16 of those which appeared in the literature up to his review in 1935.

In order to evaluate the etiologic relationship of syphilis and pulmonary arteriosclerosis, Brenner analyzed 65 recorded cases of syphilis of the pulmonary arteries. In these the large vessels were usually involved. In only 2 were the small vessel changes possibly regarded as syphilitic. In only 15 of the 65 cases was the syphilitic nature of the arterial disease reasonably well established, and of these, there were 7 in which there were aneurysms of the pulmonary artery. Spirochetes were found in 2 instances, in Warthin's[12] case, and in one of the cases reported by Arrillaga[2], where they were found in the peribronchial and lymphoid tissue. One case of syphilis of the pulmonary artery, reported by Brenner[7] showed histologic changes similar in all essential respects to the changes found in the aorta in the patient who furnished the reason for this report. The pathologic findings in our case are at variance

with Brenner's[7] statement that "syphilis of the pulmonary arteries is essentially a disease of the larger vessels in spite of all that has been written on the importance of pulmonary endarteritis obliterans in the production of symptoms."

Ayerza's Disease. It is generally agreed that a precise meaning of this term has not been established. It has been used by some to mean any condition of cardiac failure associated with presumed pulmonary vascular disease, and by others it has been identified with primary pulmonary arteriosclerosis.

The role played by syphilis in the etiology of Ayerza's disease has been a subject of speculation and of study of all who have written on this subject. In Arrillaga's[2] report there were 7 cardiac patients with intense cyanosis *(Cardiacos negros)*; 5 had strongly positive Wassermann reactions; one, with no Wassermann test recorded, had a history of a primary lesion. In 1 instance the Wassermann was negative. Autopsies in 5 cases showed aneurysm of the pulmonary artery in 2, rupture of the pulmonary artery into the pericardium in 1, and atheromatous changes in the pulmonary artery, with hypertrophy and dilatation of the right ventricle, in 2.

It is obvious that syphilis played a major etiologic role in these cases. In 1913, Arrillaga[3] expressed the opinion that the chief cause of Ayerza's disease was chronic respiratory disease with emphysema, and that a chronic infection such as syphilis sensitized the vascular system. Subsequently[4], he reached the conclusion that the essential factor in Ayerza's disease was syphilis, and that chronic pulmonary infection and, or, cardiac disease favored localization of the syphilitic process. It is patently fruitless to attempt to draw conclusions from such theoretical statements. Barlaro[5] in 1917 stated that there are many causes for Ayerza's disease, but syphilis is the commonest. Brachetto-Brian[6] in 1925 stated that in Ayerza's disease syphilis is often present even when the pulmonary and vascular lesions are not syphilitic. It would be pertinent to inquire how he reached this conclusion.

Moschcowitz[11] is of the opinion that "so-called Ayerza's Disease" is a syndrome developing from any lesion causing hypertension and consequent arteriosclerosis of the lesser circulation. He does not regard it as proven that there is a constant relationship between syphilis and this disease.

It would appear that Ayerza's disease occurs most frequently in a syphilitic who *also* has some chronic infection of the lower respiratory tract. There are many different kinds of infection of the bronchial and pulmonary tissues, with or without pulmonary emphysema, which in the presence of syphilis may produce the clinical and pathologic picture designated "Ayerza's disease". Because of our lack of precise knowledge of the etiology of this condition, it would seem that the term "Ayerza's syndrome" is to be preferred.

The etiologic relationship between syphilis and Ayerza's disease is tersely summarized by Brenner[7] in the following statement: "Syphilis of the pulmonary arteries may be suspected if in a syphilitic patient there is heart failure, with or without marked cyanosis, with enlargement of the right ventricle as determined by physical examination and by x-ray, and by the electrocardiogram, graphic evidences of right ventricular preponderance". He further stated that these requirements were not fulfilled in most of the reported cases.

In our opinion, the following report meets Brenner's diagnostic criteria:

Case Report. C. E., white, male, aged 48, was admitted to this hospital on 6 occasions between July, 1495, and the time of his death in September, 1947. His history was that of increasing dyspnea for a year prior to his first admission. He also had a chronic cough of many years duration. He had had no orthopnea, and no hemoptysis. At the time of his first admission on July 27, 1945, the pertinent findings were a normal temperature, with persistent tachycardia and a moderate increase in respiratory rate. The blood pressure was 148/106. He was dyspneic at rest, markedly so on slightest exertion; there was dusky cyanosis of the face and of the extremities. The heart was enlarged, especially to the right. There was no clubbing of the fingers or toes. There were subcrepitant rales all over both lungs. The blood count was: hemoglobin, 117%; erythrocytes, 6 million; leukocytes, 12,400. The blood Wassermann test, Kolmer and Kline modifications, was strongly positive. The spinal fluid, colloidal gold, and Wassermann tests were negative. The sputum contained no tubercle bacilli and no fungi. Bacterial culture revealed the usual nonspecific flora. The chest roentgenogram (Dr. Pendergrass) showed a large heart with increased prominence of the right hilum shadow. There was an old, probably tuberculous, scar at the right apex, and lipoidol retention from lung mapping, done elsewhere, 5 weeks previously. The electrocardiogram (Dr. Wolferth) showed right ventricular hypertrophy and slight, right intraventricular conduction defect. By roentgenogram, there was no evidence of abnormal pulsations in the pulmonary arteries. Bronchoscopic examination (Dr. Atkins) showed generalized tracheobronchitis with marked inflammatory changes in both main bronchi. The ballistocardiogram (Dr. Starr) was reported as follows: "The ballistocardiogram is most unusual. The respiratory variation is exaggerated. The smaller systolic complexes in the respiratory cycle are normal in form, but the larger are abnormal as if increased filling of the right ventricle brought out an abnormality." Because of this patient's positive Wassermann reaction and also because he was thought to have chronic, nonspecific infection of his respiratory tract, he was given a total of 2,900,000 units of penicillin. He was discharged on August 21, 1945, with the diagnosis of pulmonary arteriolosclerosis (Ayerza's disease), either luetic or secondary to chronic, nonspecific bronchial infection.

He was readmitted on January 3, 1946, for repetition of lung function studies. He was admitted for the third time on April 14, 1946, to determine the sensitivity of the bacteria isolated from the sputum to penicillin and streptomycin, and on the basis of these tests he was given a second course of penicillin in the amount of 2,400,000 units. His fourth admission was on July 29, 1946. The roentgenogram of the chest (Dr. Pendergrass) showed no essential change. At this time, one of the group of bacteria in the sputum was found to be moderately sensitive to streptomycin and he therefore was given 6,000,000 units of streptomycin by aerosol for 10 days. He was readmitted on March 24, 1947, for treatment of cardiac failure, probably induced by a recently acquired bronchopneumonia. He responded favorably to penicillin and oxygen. The electrocardiogram (Dr. Wolferth) at this time showed "Minor grade

TABLE I.—RESULTS OF TESTS OF PULMONARY FUNCTION

	Normal Values	*Aug. '45*	*Jan. '46*	*May '46*	*Sep. '46*	*Apr. '47*
Arterial oxygen saturation	98%	90	92	91	84	—
Plasma CO_2 (vols. %)	59	48	52	51	46	—
Arterial CO_2 tension (mm. Hg)	40	34	36	34	29	—
Arterial pH	7.42	7.42	—	7.44	7.44	—
Volume Respiration (liters/min.)	7	16.0	8.8	10.4	12.8	—
Vital capacity (cc)	3500	2500	2460	2650	2310	—
Max. voluntary ventil. (l./min.)	150	64	79	—	—	—
Oximeter rate	50"	100"	—	300"	—	330" *

* On April 1, 1947, his nitrogen elimination rate, pulmonary gas mixing and respiratory air velocities were within normal limits.

heart block (no digitalis). The larger P waves in CR_2 and CR_3 suggest right auricular hypertrophy.[5] His final admission was on July 27, 1947, again for the treatment of cardiac failure and bronchopneumonia. He responded to oxygen therapy. During the 2 years that this patient was under observation, it was found that the only drug which provided sufficient symptomatic relief to permit him to continue at work was potassium iodide (2 cc. of a saturated aqueous solution 3 times a day). On numerous occasions the drug was stopped, but it was never possible to withhold it for more than 48 hours. In this connection, it is of great interest that hypertension due to constriction of the pulmonary vessels. The low CO_2 and CO_2 tension are due to hyperventilation. This cannot be due entirely to oxygen lack, for the inhalation of 100% oxygen did not reduce the respiratory minute volume to normal. This indicates that there is a pulmonary lesion, either alveolar or vascular, setting up vagal Hering-Breuer reflexes stimulating breathing. The low arterial CO_2 tension is definitely against the diagnosis of emphysema, for CO_2 tension is almost invariably above normal in this disease. Upon inhalation of 100% oxygen, the oxygen saturation rose from 89 to 100%, therefore the pulmonary blood flow is fast

FIG. 1. Heart showing marked hypertrophy of the right ventricle, the wall of which measures 10 mm.

Arrillaga[2] (1912), writing on the treatment of Ayerza's disease, stated that even if syphilis is not present, iodides seem to be of great value in the treatment of these patients. In September, 1947, the patient was confined to bed at home because of marked dyspnea and dependent edema. He expired suddenly on September 10, 1947.

PULMONARY FUNCTION STUDIES. Table 1 lists some of the tests for pulmonary function performed by Dr. Julius H. Comroe, Jr. The first study on August 9, 1945, was interpreted by Dr. Comroe as follows: "These tests are consistent with the diagnosis of pulmonary enough to saturate the arterial blood. This and the low vital capacity lead me to believe that there is some decrease in the functioning lung tissue."

Subsequent studies by Dr. Comroe and Dr. Ward S. Fowler were interpreted similarly. It was of considerable interest that the interpretations of the tests of pulmonary function were essentially in agreement with the necropsy findings.

NECROPSY (by Dr. Camp). The body was embalmed about 16 hours before necropsy at this hospital, as the patient had died outside of Philadelphia. *Heart* (570 gm.). It is

hypertrophied, mostly on the right. The right auricle is dilated, and the right ventricle is dilated and hypertrophied; the wall measures 10 mm. The left auricle is somewhat dilated, and the left ventricle somewhat hypertrophied. The wall measures 15 mm. The heart valves and the mural endocardium present no lesions. The coronary arteries present a few yellow intimal plaques which do not narrow the lumen significantly. The myocardium is firm and reddish brown and there are no areas of softening or scarring.

FIG. 2. Section of aortic wall to illustrate changes compatible with syphilis. Verhoeff elastic tissue stain (x 155).

The *aorta* shows perivascular lymphatic infiltration in the adventitia, interruption of the elastic fibers in the media, and thickening of the intima. While these changes are not of great magnitude, they are taken to be compatible with syphilis.

Lungs. The right weighs 660 gm., the left 500 gm. They are well fixed with embalming fluid. There are several small (1 to 2 cm.) sub-pleural blebs in each lung. The tissue is crepitant throughout and there are no palpable consolidations or nodules. The pulmonary arteries are dilated, and on cut section the smaller arteries stand out and their walls show increased thickness. The bronchi reveal no lesions. Histologically, there is intimal arteriosclerosis of the large and medium sized arteries, and a moderate degree of pulmonary emphysema.

The other organs of the body were grossly normal. Histologically, the *liver* showed chronic passive congestion and fatty dystrophy, and the *spleen* showed chronic passive congestion. The microscopic examination of one of the *skeletal muscles*, the gastrocnemius, showed no arteriosclerosis. The brain and spinal cord were not examined. The *kidneys* were normal in size and shape, the capsules stripped with ease revealing a smooth, reddish brown surface over which there were several depressed flattened scars. These on microscopic examination proved to be small areas of healed pyelonephritis.

Comment. Despite the universality of pulmonary arteriosclerosis in adults, the clinical syndrome designated "Ayerza's disease" is a relatively uncommon condition and cannot result solely from those pulmonary vascular changes which are invariably present in early adult life and inexorably progress with advancing years. Chronic cardiac disease, especially mitral stenosis, pulmonary emphysema, and long-standing infection of the respiratory tract unquestionably accelerate the rate of development, and intensify the degree of pulmonary arteriosclerosis, but despite this, they are rarely capable of producing sufficient obstruction in the pulmonary circulation to cause Ayerza's disease.

It is very doubtful that syphilitic infection alone is a frequent cause of Ayerza's disease, if one compares the tremendous difference in the respective incidence of these diseases. However, one cannot ignore the fact that syphilis is found much more often in cases of Ayerza's disease than can be explained by coincidence. A careful review of the literature with particular reference to the case reports of Ayerza's disease which satisfy most of the diagnostic criteria, leads to the conclusion that this disease occurs most frequently in the syphilitic. In the present state of our knowledge, there is no way of proving that the lesions in the pulmonary arterioles are syphilitic. Only once have *Treponema pallida* been reported in the wall of the pulmonary artery (Warthin's case), and in no recorded instance have they been seen in the pulmonary arterioles. Conceding that syphilis is not the sole cause of Ayerza's disease, although it occurs most frequently in the syphilitic, it is pertinent to search for other

FIG. 3. Lung showing 2 small arteries, each of which shows intimal proliferation with reduction in the size of the lumen. Verhoeff elastic stain (x 275).

etiologic agents which, in the presence of syphilis, most often produce the clinical picture described as *Cardiacos negros*. The majority of the recorded cases of Ayerza's disease, in addition to having syphilis, also have chronic infection of the lower respiratory tract, with or without some degree of emphysema. It is doubtful if chronic cardiac disease alone, including even mitral stenosis, causes sufficient pulmonary arteriolosclerosis to produce Ayerza's disease, and it is extremely doubtful if emphysema alone can ever do so. The most that can be said at the present time is that Ayerza's disease occurs most frequently in a syphilitic who also has chronic infection of the lower respiratory tract. The term "Ayerza's syndrome" is to be preferred to the designation "Ayerza's disease" in the present state of our lack of precise knowledge of the etiology of this condition.

Summary and Conclusions. The disease picture and the etiology of Ayerza's disease have been considered as found in the literature of the past half-century. A case report has been presented which clinically fulfilled all of the essential diagnostic criteria.

Studies of pulmonary function were diagnostically significant in that they tended to rule out significant pulmonary emphysema, and indicated the presence of a pulmonary lesion, either

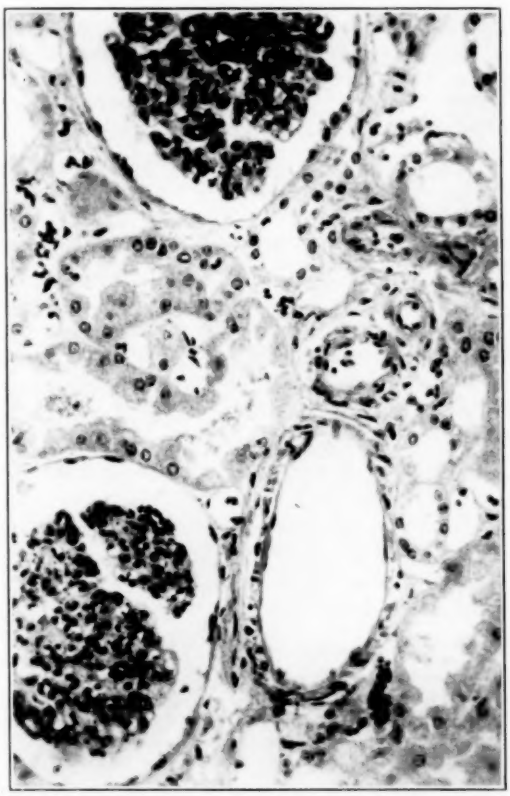


FIG. 4. The kidney showing an arteriole without the intimal proliferation seen in the lung vessels. H and E (x 275).

alveolar or vascular, causing decrease in functioning lung tissue. At necropsy, there were changes in the aorta compatible with syphilis; there was marked hypertrophy of the right ventricle, and intimal proliferation of the small pulmonary arteries with reduction in their lumen. Similar changes were absent from the small vessels of the greater circulation.

In our opinion, this condition occurs most frequently in an individual with syphilitic infection, who has in addition to this disease a chronic infection of the lower respiratory tract. Because of lack of more precise knowledge of the etiology of this disease, it is suggested that "Ayerza's syndrome" would be a more proper designation for the clinical picture.

The author desires to express his appreciation to Dr. A. J. Rawson for his description of the photomicrographs, and to Dr. Herman Gold for his translation from the Spanish of Arrillaga's monograph on Cardiacos negros.

REFERENCES

1. **Alexander, H. L., Luten, D.,** and **Kountz, W. B.:** J. Am. Med. Assn., **88,** 882, 1927.
2. **Arrillaga, F. C.:** Esclerosis Secundaria de la Arteria Pulmonar y su Cuadro Clinico (Cardiacos negros), Buenos Aires, 1912.
3. **Arrillaga, F. C.:** Arch. d. mal du coeur, **6,** 518, 1913.
4. **Arrillaga, F. C.:** Bull. et mém Soc. méd. d. hóp. de Paris, **48,** 292, 1924.
5. **Barlaro:** Rev. d. l. Asoc. Argentina, **26,** 121, 1917.
6. **Brachetto-Brian, D.:** Rev. Soc. de Med. int. y Soc. de Tisiol, **6,** 821, 1925.
7. **Brenner, O.:** Arch. Int. Med., **56,** 211, 457, 724, 976, 1935.
8. **Escudero:** Conferencias Clinicas, Buenos Aires, 1905.
9. **MacCallum, W. G.:** Bull. Johns Hopkins Hosp., **49,** 37, 1931.
10. **Marty, C. A.:** La Tension Arteriel en la Tuberculosis Pulmonar, p. 45, Buenos Aires, 1909.
11. **Moschcowitz, E.:** Am. J. Med. Sci., **174,** 388, 1927.
12. **Warthin, A. S.:** Am. J. Syph., **1,** 693, 1917.

GLUCOSE TOLERANCE: I. A COMPARISON OF 4 TYPES OF DIAGNOSTIC TESTS IN 103 CONTROL SUBJECTS AND 26 PATIENTS WITH DIABETES

By John H. Moyer, M.D.§

AND

C. Ray Womack, M.D.†

FORT SAM HOUSTON, TEXAS

(From the Medical Service, Brooke General Hospital)

As early as 1913 observations[1] on the blood sugar level and its relation to the ingestion of carbohydrate suggested new approaches to the clinical study of carbohydrate metabolism. Four years later Hamman and Hirschman[12] conceived the idea of following the blood sugar level after a standardized oral dose of glucose, and proposed this procedure as a clinical test for the evaluation of carbohydrate metabolism. Numerous variations of this method have been developed and employed as means of estimating the patient's ability to utilize carbohydrate. At present the most widely used tests are the 1 dose oral ("standard") test, the 1 hour, 2 dose test of Exton and Rose[8], and the intravenous test. The postprandial blood sugar level, determined 2 to 2½ hours following a standard meal, is sometimes used.

The present study was initiated because of difficulties encountered in evaluating Army patients with suspected diabetes mellitus, in that discrepancies in the diagnostic implications of results obtained when using the various types of tolerance tests were often noted. This difficulty was accentuated by the exacting diagnostic conclusions required by disposition and retirement boards. In an attempt to determine the significance of these inconsistencies in the results of tolerance tests, a control group of 103 persons having no discernible disturbance of metabolism (Group 1), 26 patients with frank clinical diabetes (Group 2), 29 patients with liver disease (Group 3), and 71 persons admitted to the hospital because of asymptomatic glycosuria discovered on routine urinalysis (Group 4), were given the 3 types of tolerance tests*, that is, the standard 1 dose oral test, the 1 hour, 2 dose test, and the intravenous test. Most of the subjects also had a postprandial blood sugar determination 2 hours after a standard meal.

Material. The 103 control subjects consisted of hospital personnel and of ambulatory patients hospitalized for orthopedic conditions, uncomplicated duodenal ulcer, and otorhinologic disease. All but one of these individuals were males. The average age was 28 years, with a range of 17 to 68 years. Ten patients were older than 50 years. Only 1 case exceeded 60 years of age, a factor of significance in view of the decreased glucose tolerance noted at times in old age[6]. Since decreased tolerance in obese individuals, presumably resulting from impaired glycogenesis[4], has been noted by many observers[13,25], no obese persons were used in this group. A few had weights exceeding the average for

* Of the 71 patients with glycosuria 25 were not given an intravenous test.

§ Present address: Baylor University, Department of Medicine, Houston, Texas.

† Present address: Vanderbilt University, Nashville, Tennessee.

their height and age by more than 20%. Three subjects exceeded the average by 25% or more, but these patients were exceptionally tall and large-framed, and were not clinically obese. None in the group had a family history of diabetes.

The diagnosis of diabetes mellitus in the *diabetic* group of 26 persons was made on the usual clinical bases, exclusive of tolerance tests. No reasonable doubt as to diagnosis was felt to exist. Tolerance tests were performed prior to any treatment with diet or insulin.

The findings in the 29 patients with liver disease have been presented elsewhere[24]. A consideration of patients with glycosuria will be reported in a future communication.

immediately given another 50 gm. of glucose. A blood and urine sample was obtained ½ hour later and, in a few cases, 1 hour later still.

Intravenous Test. The fasting blood and urine specimens were secured and the subject was given an intravenous infusion of 0.5 gm. of glucose per kg. of ideal body weight**. The glucose was dissolved in 300 cc. of normal saline, and administered over a minimum of 20 and a maximum of 30 minutes. Urine specimens and blood samples were obtained ½ hour, 1 hour, 2 hours, and 3 hours after starting the infusion.

The Postprandial blood sugar determinations were done 2 hours after a standard

TABLE. 1.—STATISTICAL SUMMARY OF RESULTS ON 103 CONTROLS AND 26 PATIENTS WITH DIABETES*

	Standard Test					*Exton-Rose Test*					*Intravenous Test*					*Post-*
	F	*½ hr.*	*1 hr.*	*2 hr.*	*3 hr.*	*F*	*½ hr.*	*1 hr.*	*2 hr.*	*F*	*½ hr.*	*1 hr.*	*2 hr.*	*3 hr.*	*Prand.***
CONTROL—103 PATIENTS															
Mean (M_1)	96	145	128	96	82	98	138	132	93	96	224	127	88	91	98
Standard Deviation (S. D.)	11	25	30	15	16	11	25	34	12	11	69	41	13	13	18
DIABETES—26 PATIENTS															
Mean (M_2)	154	272	325	323	255	179	280	345		164	367	297	223	185	248
Standard Deviation (S. D.)	65	106	98	119	121	70	87	113		63	75	86	95	95	117

* $S.D.(Series) = \sqrt{\frac{\Sigma X^2 - M^2}{N}}$ Calculations made by Capt. J. A. Rafferty, Randolph Field, Texas, and Dr. Margaret P. Martin, Dept. of Preventive Medicine, Vanderbilt Univ.

** Includes only 97 of the control group and 22 of the 26 patients with diabetes.

Note: F Ratios showed the highest significant difference at the 2 hour period in both the standard and the intravenous tests, 2.2 and 1.8 respectively.

Techniques. *Standard Oral Test* (1 Dose). A fasting blood and urine sample was obtained following which the subject was given 100 gm. of glucose in 600 cc. of water flavored with lemon juice. Blood and urine specimens were obtained at intervals of ½ hour, 1 hour, 2 hours, and 3 hours following ingestion of the sugar.

1 Hour, 2 Dose Test (Exton-Rose). A fasting blood and urine specimen was obtained. The subject was then given 50 gm. of glucose in 300 cc. of water flavored with lemon juice. One-half hour later a blood and urine sample was secured, and the individual was

meal consisting of 100 gm. of carbohydrate, 35 gm. of protein, and 35 gm. of fat.

All tests with the exception of the postprandial blood sugar determinations were done in the morning after a 12 hour fast. All patients in this study were allowed full activity about the hospital. However, these activities were restricted to the hospital in order to avoid physical exertion of a marked degree. The patients, with the exception of a few with diabetes, were placed on a standard 2,400 calorie diet consisting of 280 gm. carbohydrate, 100 gm. protein, and 100 gm. fat (approximately equivalent to 350 gm. of

** In cases in which this amounted to less than 25 gm. of glucose, the subject was given a 25 gm. dose.

available carbohydrate per day: Dextrose = CHO + 0.58P + 0.1F). The subjects received this diet for a minimum of 5 days before testing. The value of a preparatory diet adequate in carbohydrate prior to testing is well known[3]. In view of the reported increase in tolerance as a result of repeated testing[19], a minimum of 2 days was allowed between successive tests. This interval was 4 to 6 days in the majority of instances.

Venous blood, drawn within 20 sec. after the application of a tourniquet, was employed for analysis. Quantitative blood sugar analyses were made by the technique of Folin and Wu[9], using a photoelectric colorimeter. Qualitative urine sugar concentrations were estimated in all patients by Benedict's method[2]. The statistical data obtained on the 103 control subjects (Group 1) and the 26 patients with unequivocal clinical evidence of diabetes (Group 2) are summarized in Table 1.

Discussion. Despite the fact that glucose tolerance tests have been used for many years, have been performed on many individuals—both normal and ill—and have been found clinically useful as diagnostic measures, differences of opinion exist as to which test is preferable and what constitutes a normal or a significantly abnormal test[15]. These facts would appear to warrant the present study in which the 4 testing techniques in common use are employed on the same normal individuals, followed by the application of these techniques and results to the abnormal.

Evaluation of the Normal 1 Dose Oral ("Standard") Test: The upper limit of normal for the fasting blood sugar in the control group was 118 mg. per 100 cc. when M+2 S.D. was used (Table 1). One individual exceeded this level by 2 mg. Therefore the assumption by many observers[7,13], that 120 mg. per 100 cc. represents the normal upper limit seems valid, although an occasional fasting level as high as 129 mg. (M+3 S.D.) might be expected. Contrariwise, only 17 (65%) of the 26 diabetic patients exceeded this level, thus invalidating the fasting blood sugar as a critical determination in the evaluation of abnormal carbohydrate tolerance.

The standard curve in the control group generally shows a moderately rapid rise to a peak level at the end of ½ hour. In 18 of the 103 cases, the maximum was attained more slowly, the peak occurring at 1 hour; and in 8 cases the ½ hour and 1 hour levels were equal. These differences in rapidity of attaining peak levels may be related to gastric emptying time[33]. In this control series the mean peak occurred at ½ hour with a value of 145 mg. per 100 cc. and a standard deviation of 25. Considering the normal range of the peak blood level to lie within 2 S.D. of the mean, the height of the curves could be expected to reach 195 mg. Three to 5% might be expected to reach 220 mg. (3 S.D.). Table 2 (items 8, 9, and 10) demonstrates that, in the control group, a considerable number of persons had standard curves peaking above levels considered by different observers to represent evidence of diabetes. The actual range for the entire group was 89 to 223. A level of 180 mg. was exceeded by 11% of the individuals. All except one diabetic subject rose above 180 mg. In view of the facts that normal individuals may be expected to reach a peak of at least 195 mg. (2 S.D.), and a few may rise as high as 220 mg., and that many adjustments incident to absorption, distribution, and excretion of glucose are taking place during the first hour of the test, we believe that the height of the curve is of little or no diagnostic significance[15,18]. In addition, we have not found it to be of great value in determining the severity of diabetes, as reported elsewhere[35], though such a relationship might logically be assumed to exist.

The peak is followed by a steady decline to normal levels by 2 hours.

TABLE 2.—COMPARISON OF ABNORMAL RESULTS OF 3 TYPES OF TOLERANCE TESTS AND OF THE POSTPRANDIAL BLOOD SUGAR ACCORDING TO VARIOUS CRITERIA†

Item No.	*Criterion*	*Test Involved*	*103 Controls*		*26 Diabetics*	
			No.	*%*	*No.*	*%*
1.	Fasting Sugar above 120 mg./100 cc.	Stand.	0	0	17	65
2.	2 hr. sugar above 120 mg.[18]	"	0	00	26	100
3.	2 hr. sugar above fasting level[13]	"	45	44	25	96
4.	2 hr. sugar above 110 mg.	"	18	18	26	100
5.	*2 hr. sugar above 125 mg.**	"	*0*	*0*	*26*	*100*
6.	*2 hr sugar above 140 mg.***	"	*0*	*0*	*26*	*100*
7.	3 hr. sugar above fasting level[14]	"	17	17	22	85
8.	Peak level above 160 mg.	"	28	27	26	100
9.	Peak level above 170 mg.[13]	"	18	18	26	100
10.	Peak level above 180 mg.[16]	"	11	11	25	96
11.	Fasting sugar above 120 mg./100 cc.	1 hr.—2 dose	0	0	21	81
12.	Rise over 75 mg. from fasting to ½ hr. specimen.[8]	"	9	9	19	73
13.	Rise over 5 mg. but less than 10 mg. of the 1 hour above the ½ hr. level.[8]	"	2	2	0	0
14.	Items 12 and 13 both present	"	0	0	18	69
15.	Rise over 10 mg. from ½ hr. to 1 hr. specimen—Exton and Rose.[8]	"	23	22	24	92
16.	Rise over 50 mg. from fasting to ½ hr. specimen.[11]	"	29	28	22	85
17.	Rise over 30 mg. from ½ hr. to 1 hr. specimen.[11]	"	7	7	20	77
18.	Items 11 and 16 both present.[11]	"	0	0	17	65
19.	Items 11 and 17 both present.[11]	"	0	0	17	65
20.	Items 11, 16 and 17 present.[11]	"	0	0	14	54
21.	Items 16 and 17 both present.[11]	"	2	2	17	65
22.	Diabetic according to criteria of Gould *et al.*[11]	"	2	2	22	85
23.	*1 hr. sugar above 158 mg. Mathews et al.*[22]	"	*16*	*16*	*25*	*96*
24.	*1 hr. sugar above 180 mg. Mathews et al.*[22]	"	*6*	*6*	*25*	*96*
25.	Fasting sugar above 120 mg./100 cc.	I.V.	0	0	20	77
26.	*2 hr. sugar above 114 mg.**	"	*2*	*2*	*25*	*96*
27.	*2 hr. sugar above 127 mg.***	"	*0*	*0*	*23*	*89*
28.	2 hr. sugar above 120 mg. Kolmer.[18]	"	0	0	23	89
29.	2 hr. level above the fasting level.[17]	"	22	21	22	85
30.	*Level above 134 mg./100 cc.**	*P.P.*	*3*	3***	*21*	*96****
31.	*Level above 151 mg.***	"	*1*	*1****	*19*	*86****
32.	Level above 160 mg.	"	0	0***	17	77***
33.	Level above 170 mg.	"	0	0***	16	73***

* Author's criterion for upper limit of normality (M + 2 S.D.).

** Mean + 3 S.D. according to the author's observations. Beyond this range the test is regarded as diabetic in type.

*** Postprandial blood sugar levels were determined on only 97 controls, 22 diabetics. Percentages refer to precentage of the group on which the test was performed.

† Raw data to be published elsewere.

Although a fairly striking hypoglycemic phase was noted in many normal individuals, secondary hyperglycemic "rebound phenomena" previously noted by others[10] were not observed. This may be related to the infrequent sampling during the 2nd and 3rd hour period in our studies. The hypoglycemic phase is generally attributed to over-secretion of insulin as a result of the hyperglycemic stimulus to the pancreas. However, Soskin[27] denies the primacy of increased pancreatic activity, and presents evidence of an inherent hepatic "homeostatic mechanism" which, after being stimulated into activity by hyperglycemia, fails to become arrested immediately upon the return of the blood sugar to normal levels. This hypoglycemic phase was noteworthy, particularly at the 3 hour period and somewhat after 4 hours when blood samples were taken at this time. Twenty-five patients exhibited levels of 70 mg. per 100 cc. or below at 3 hours, 14 of whom had levels ranging as low as 50 to 60 mg. 3 hours after the ingestion of glucose. None dropped below 50 mg.

The rapidity with which glucose is removed from the blood and consequently the duration of hyperglycemia following the ingestion of glucose appears to be the most important consideration in demonstrating disturbed carbohydrate metabolism. Joslin[13] points out that the blood sugar level should have reached the fasting value by the second hour. Gould and associates[11] take as a normal curve one that has a 3 hour blood sugar below the fasting level. In the control group of the present series the criteria of these authors for a normal tolerance test were exceeded by a sizable portion of the subjects (Table 2, items 3 and 7). If one notes variability in the fasting sugar levels in the control group as well as a similar finding after 2 and 3 hours during the oral test, it appears invalid to assume that the blood sugar must consistently fall below the fasting level after either 2 or 3 hours since wide variations with respect to each other would appear to be physiological. Contrariwise, 4 of the diabetic group fell below the fasting level after 3 hours.

Regardless of these varied opinions, most investigators agree that by the end of the second hour of the test the blood sugar should have dropped to an absolute value of 120 mg. per 100 cc. or less[7,12,13]. Lawrence[18] considers that if the blood sugar has returned to normal after 2 hours, and if the fasting blood sugar is normal, the case is nondiabetic regardless of the intervening glycemia and glycosuria. The control group in the present study showed a mean 2 hour sugar level of 96 mg. per 100 cc. with a S.D. of 15 mg. The 2 hour range, using M+2 S.D., is 66 to 126 mg. (actual range: 64 to 120 mg.). Using 3 S.D., the level might be expected to reach 141 mg. in a few instances. In view of the close parallelism between the actual 2 hour range and that obtained by employing 2 S.D. from the mean, and the fact that the use of 2 S.D. includes 95% of the individuals, we believe that levels between 125 mg. (2 S.D.) and 140 mg. should be regarded as presumptively abnormal and that levels above 140 mg. (3 S.D.) should be judged definitely abnormal (diabetic). At 3 hours, using M+2 S.D., values might be expected to range up to 114 mg. (highest actual value, 119 mg.). However, in view of the fact that many persons with mildly decreased tolerance may show normal fasting and 3 hour levels, as has been noted previously[21], we feel that the 3 hour level is not critical and that its use as a diagnostic criterion might cause mild cases of diabetes to be missed. Our experience suggests that it is of value in estimating the severity of the

metabolic disturbance. These observations merely confirm the usually accepted assumption that the absolute 2 hour blood sugar level (120 to 125 mg.) in the 1 dose oral test is the critical observation. In addition the maximum blood sugar "rise" appears to be of little consequence. The fasting blood sugar should be below 120 mg. According to our observations other criteria for interpretation of this tolerance test appear to be invalid (Table 2). Using these criteria, all of the patients with diabetes had "diabetic type curves," whereas none of the control group fell into this category.

Evaluation of the 1 Hour, 2 Dose Test (Exton-Rose). Exton and Rose[8] developed the technique of the 1 hour, 2 dose oral test as it is used today, basing their approach on the Hamman-Hirschman[12] or Staub-Traugott[28] phenomenon and upon Allen's paradoxical law of glucose utilization. According to these authors, the criteria for a normal response to the 2 dose test are: 1. A fasting specimen within normal limits. 2. A rise in blood sugar not exceeding 75 mg. at the end of ½ hour. 3. Blood sugar in the 1 hour specimen less than, equal to, or not exceeding the ½ hour specimen by more than 5 mg. 4. All urines qualitatively negative for sugar. The diabetic response consists of: 1. A rise in blood sugar of 10 mg. or greater following the second dose of glucose. 2. Blood and urine sugars proportional to the severity of the disease. Robinson and co-workers[26] following these criteria, noted that 60.8% of all patients admitted to the hospital for any cause would be classified as diabetic. Gould, Altshuler, and Mellen[11] found that the criteria of Exton and Rose gave 100% correlation with the clinical diagnosis in their group of *diabetics*, but that 36.3% of their *normal controls would also be considered diabetic* by the same standards. They, therefore, modified the interpretation of the test, thinking that a diagnosis of diabetes was justified if any 2 of the following 3 conditions existed (Table 2): 1. Fasting blood sugar above 120 mg. per 100 cc. 2. A difference of 50 mg. or more between the fasting and ½ hour specimens. 3. A difference of 30 mg. or more between the ½ hour and 1 hour specimens. By these criteria they felt the test to be 97% sensitive and 100% specific, while the criteria of Exton and Rose were regarded as being 100% sensitive, but only 50% specific.

Matthews, Magath, and Berkson[22] studied the results of the 2 dose test, using a group of 117 normal controls, 304 patients with diabetes, and 70 patients with renal diabetes. These authors point out that since the only requisite for a diagnosis of diabetes, according to Exton and Rose, is a difference of 10 mg. per 100 cc. or more between the ½ hour and 1 hour levels, many non-diagnostic curves exist, as fasting levels above 120 mg. and, or, rises in blood sugar greater than 75 mg. at ½ hour and, or, 1 hour levels exceeding ½ hour levels by more than 5 but less than 10 mg. They noted also that by the criteria of Exton and Rose 54.5% of all their normal patients would be classed as diabetic. However, using the criteria of Gould and associates, many non-diagnostic curves were also found. In Matthews' series results were 88% in agreement with clinical findings using the criteria of Exton and Rose and 73% agreed under Gould's criteria. He obtained 98% agreement by using the critical level of 158 mg. at 1 hour as the diagnostic criterion. Therefore, his group considers this level the most effective criterion for differentiating the normal and the diabetic by means of this test. They state that 1 hour levels above 158 mg. denote probable diabetes and that, when the level exceeds 180 mg., a diagnosis of diabetes

can be made with assurance. The critical level of 160 mg. is, perhaps, the most widely accepted criterion of the 2 dose test at the present time for differentiating normality versus abnormality[7].

In the present series the *mean* blood sugar values (Table 1) in the control group are normal by the criteria of Exton and Rose, Gould *et al.*, and Matthews *et al.* However, Table 2 demonstrates that by the criteria of Exton and Rose only 67% (69 subjects) of results in the control group were normal. Twenty-three subjects showed diabetic curves (item 15, Table 2) and 11 patients showed non-diagnostic curves (items 12 and 13). Of the diabetic group 92% showed diabetic type curves thus demonstrating fairly high sensitivity, but low specificity. Using Gould's criteria, 65% (67 cases) of results were normal. Two patients showed diabetic curves (items 22) and 34 patients showed non-diagnostic curves (item 16, plus item 17, less item 21). In the diabetic group 22 (85%) patients would be classified as diabetic, whereas 4 would be non-diagnostic, thus demonstrating a low specificity as well as a high percentage of false positive results. Matthews' critical level of 158 mg. was exceeded by only 16 subjects, (item 23) in the control group. The 1 hour level of 180 mg. was exceeded by 6 persons, who would be considered definitely diabetic by his interpretation (item 24), so that the remaining 10 patients with levels between 158 and 180 mg. must be considered to have presumptively diabetic or non-diagnostic curves. The use of Matthews' criteria results, therefore, in a total of 16% diabetic or non-diagnostic tests in this presumably normal group and in 84% normal results. In the diabetic group, 25 (96%) demonstrated diabetic curves. Although these criteria are subject to objections, they are most specific, and give the greatest percentage of "non-diabetic" 1 hour, 2 dose curves in this group of normal controls. We do not wish to propose diagnostic criteria for this test, for reasons to be presented presently. For purposes of comparison with other tests Matthews' criteria will, therefore, be employed in this communication as the most reliable for the interpretation of the 1 hour, 2 dose test.

Evaluation of the Intravenous Test. Tolerance testing by the administration of sugar directly into the blood stream has been developed and various techniques described. Despite the criticism[19] that the method is unphysiological, especially as the glucose is administered into the systemic circulation, and not into the portal system, thus by-passing the liver, the technique has enjoyed some popularity. The oral type of test fails to differentiate between changes in blood sugar level resulting from abnormal gastrointestinal absorption and those due to metabolic defect. Most of the methods are based upon the studies of Thannhauser and Pfitzer[29]. The lack of agreement as to a uniform procedure in intravenous testing has been pointed out, and a survey of some of the various techniques presented by Tunbridge and Allibone[31]. Lozner, Winkler, Taylor, and Peters[21] studied the use of 50 cc. of 50% glucose, given within a 2 minute period, followed by periodic blood sugar determinations over a 3 hour period using the Somogyi zinc precipitation method. This procedure gives fermentable "true sugar" levels in contrast to the tungstate precipitation technique, such as the Folin-Wu method, which does not remove non-glucose reducing substances, largely glutathione and ergothionine. These substances are generally considered to exist at a fairly constant level amounting to about 10 to 30 mg. per 100 cc.[13]. Therefore, the Somogyi values may be expected to average approximately 20

mg. lower than those done by the Folin-Wu technique. In 60 normal individuals Lozner *et al.* found the mean 2 hour level to be 78.8 mg. with a S.D. of 7.2 mg. They considered abnormal any level at 2 hours greater than 3 S.D., that is, 100 mg. (approximately equivalent to 120 mg. by the tungstate method), and concluded that, if the 2 hour level is greater than 120 mg. (equivalent to 140 mg.), the patient probably has diabetes; if below 100 mg. (equivalent to 120 mg.), he probably does not. Levels between these 2 figures were considered non-diagnostic.

A frequently employed method, and the one used in the present study, consists in the administration of 0.5 gm. of glucose per kg. of body weight in approximately a 20% solution over a period of about 20 to 30 minutes, followed by blood sugar determinations during a period of 3 hours. The dosage of glucose approximates the quantity found by Cori and Cori[5] to be the maximal oral dose which can be absorbed by the gastrointestinal tract during the time involved. This dosage is therefore felt to be as nearly physiological as possible by the intravenous method of administration. By this method Kolmer[15] thinks that the blood sugar level should have returned to 120 mg. or below within 2 hours after starting the injection. Duncan[7] states that by the same technique the blood sugar should normally fall below the initial level at 2 hours. It was found that the control group in the present series showed a mean 2 hour level of 88 mg. with a S.D. of 13 mg. A range of 62 to 114 would be expected, using 2 S.D. By the same reasoning as that previously discussed in relation to the 2 hour level on the standard test, it would appear reasonable to assume that a few normal persons (3 to 5%) may be expected to show 2 hour levels ranging up to 127 mg. (3 S.D.) when the Folin-Wu method for blood sugar determinations is used. However, we feel that levels between 114 mg. and 127 mg. should be regarded as presumptively abnormal, and that those above 127 mg. (3 S.D.) should be considered diabetic until disproved. Lozner's 2 hour mean plus 2 S.D. yields an upper level of 93 mg. (equivalent to 113 mg. if the Folin-Wu rather than the Somogyi zinc method is used for analyses). The close parallelism between our 2 hour value and that of Lozner, corrected for the difference in analytic technique, is of interest in view of the difference in method of administration of the sugar. This would seem to imply that the dosage rather than the rate of administration is the important factor.

Our criteria for a normal intravenous test by the method used are, therefore, a normal fasting blood sugar level and a 2 hour level of 114 mg. per 100 cc. or below. Values between 114 and 127 mg. would be considered non-diagnostic and above 127 mg. as diabetic. The height of the curve here too appears to be of no diagnostic value.

Evaluation of the Postprandial Blood Sugar Level. In the control group the mean 2 hour postprandial sugar level was 98 mg. per 100 cc. with a S.D. of 18 mg. The expected range using 2 S.D. would be 63 to 134 mg., and using 3 S.D. would be 45 to 151 mg. Three persons exceeded 134 mg. on the postprandial, and only 1 exceeded 151 mg. The rather large standard deviation attests to a considerable scatter in values about the mean. Because of the variability in the factors of the amount of food consumed in the meal, variation in the rapidity of digestion, intestinal motility, absorption, and so on, concerned in relation to a meal of complex foodstuffs as compared to a monosaccharide, it seems reasonable to allow

the widest feasible range of normality in interpreting this test, realizing that the test is probably more gross and variable than those employing glucose. However, from our observations the test appears to be the easiest to perform and an excellent presumptive test. For our purposes of comparison here, we will consider values above 134 mg. as borderline, and those above 151 mg. as diabetic until proved otherwise.

Comparative Evaluation of the 4 Tests—that is, the ("Standard") 1 Dose Oral, the 1 hour, 2 dose Oral (Exton-Rose), the Intravenous Test, and the 2 hour Postprandial Blood Sugar. Having determined from the aforementioned considerations of the control data what shall be regarded as the normal results of the 4 types of tolerance tests and the best criteria for the interpretation of these results, it is of interest to compare the diagnostic implications of these tests with each other. From Table 2 it is patent that a number of individuals showed inconsistencies in the results of various tests as regards normality versus abnormality, regardless of the criteria used for interpretation of the individual test. This is especially evident in items 5 and 6 (Standard), 23 and 24 (Exton-Rose), 26 and 27 (Intravenous) and 30 and 31 (Postprandial Sugar Level) which include the most valid criteria for the interpretation of each test.

Using other criteria for the standard test previously presented and referring to Table 2, we note that the 103 control subjects fell within normal range. All 26 of the diabetic group showed diabetic glucose tolerance tests. Therefore, the standard test appears to be both highly sensitive and specific. However, these features may be more apparent than real since the diabetic group presented enough clinical evidence of diabetes to establish the diagnosis beyond a reasonable doubt. If borderline cases are analyzed we might expect a number of tests to fall within the non-diagnostic range, that is, the range represented between 2 and 3 S.D. from the normal mean (125 to 140 mg. at the 2 hour period). This will be borne out in a future communication in which the tolerance tests done on 71 patients with "glycosuria", but without clinical evidence of disturbed metabolism are analyzed. However, since the 1 hour, 2 dose test, the postprandial blood sugar test, and the intravenous test were done on this same group of 103 control subjects and 26 diabetic patients the comparison in the present communication seems justified.

The results of the intravenous test closely parallel those of the standard oral test when the 2 hour blood glucose level is used as the critical consideration. The upper limit of normal is 114 mg. using M + 2 S.D. The range between M + 2 S.D. and M + 3 S.D. is taken to be non-diagnostic (114 to 127 mg.). None of the control group fell into the diabetic range although 2 tests (119 and 120 mg.) would be considered non-diagnostic. However, borderline deviations of this degree could be considered within the range of analytical error (5 mg. for all volumetric analyses)[23]. Contrariwise, in the group of 26 frank diabetics, one displayed a normal intravenous test and 2 fell within the non-diagnostic range. In view of the degree of disturbance of carbohydrate metabolism in this group, this would not be anticipated in a highly sensitive test. Therefore, we might conclude that the intravenous is highly specific, but that the evidence suggests that it is not as sensitive as the standard oral test. This will also be borne out more conclusively in the analysis of the "asymptomatic glycosuria" group of patients who fall into a more borderline range.

The postprandial blood sugar taken 2 hours after a standard meal, like the

intravenous test, appears less specific than the standard oral test. In the control series, 2% fell into the presumptively abnormal and 1% into the frankly abnormal group. Contrariwise, in the group of 22 patients with diabetes upon whom this test was done, 2 (9%) displayed only presumptively abnormal values, and 1 (4.5%) fell within the range of normality. However, the correlation with the standard oral and intravenous tests is surprisingly good. We can conclude that in view of the simplicity of the postprandial test, it is of definite value as a tool for clinical evaluation of carbohydrate metabolism.

A great discrepancy is encountered when the results of the 1 hour, 2 dose test are analyzed and compared with the other tests. This test appears to present a prohibitive number of false positive results in the control series regardless of the criteria for interpretation used. Although the 1 hour, 2 dose test has appeared to be accurate in the hands of some investigators, when the critical level of 158 mg. at the 1 hour period is used[22], this has by no means been universally concurred in. Kelly[14] has reported that, of 82 individuals showing abnormal 2 dose test, only 53 (64.6%) had abnormal standard tests by this criterion. Langner and Dewees[16] have likewise concluded that the 1 dose test is more reliable than the 1 hour, 2 dose test.

In reference to Table 2, only 84% of the 103 controls fall into the normal range when the absolute value of 158 mg. at the 1 hour period is used as the critical level. Of the remaining 16%, 6% would be classified as frank diabetes, and 10% as "presumptively diabetic" or non-diagnostic. None of these patients exhibited abnormal standard curves according to the criteria used. At the same time all but one of the 26 diabetic patients exhibited frankly diabetic 1 hour, 2 dose tests.

The above findings strongly suggest that the 1 hour, 2 dose test is overly sensitive. Early during the study these findings led us to believe, because of the relative simplicity of performance of the test, that it might be used as an exclusion or "screen" test where large numbers of individuals were to be evaluated from the standpoint of carbohydrate tolerance. This was to be followed by standard tests in those cases showing abnormal 1 hour, 2 dose tests, in very much the way precipitation exclusion tests are used in syphilis study. However, serious objections have been made to the 2 dose procedure which might lead one to question the specificity as well as the sensitivity of the test. Lawrence[18] notes that the test, as performed, is only "vaguely reminiscent" of Staub's and Traugott's original procedures in which the second dose of glucose was given after 1 or 2 hours, rather than ½ hour, when the blood sugar level was falling or had returned to normal in non-diabetic individuals. Thus the blood sugar was raised but little by a second dose in the normal, whereas the diabetic patient showed further rise. In addition, Cori and Cori[5] point out that since an absorption of 0.99 gm. per kg. per hour was found in dogs by Trimble and coworkers[30], and an intravenous tolerance rate of 0.9 gm. per kg. per hour was determined in dogs by Woodyatt[36], a close relationship between rate of intestinal absorption and the rate of glucose utilization exists. Therefore, since the maximum rate at which glucose may be injected in man without losing glucose in the urine is 0.85 gm. per kg. per hour[34], one may infer that the maximal rate of gastrointestinal absorption in man could hardly be greater. This is equivalent to a maximum absorption of 59 gm. per hour in a 70 kg. man. Leonards and Free[20] found that in normal adult male subjects given the Exton-Rose test, from 38 to 62 gm. (average 50 gm.) of glu-

cose could be recovered from gastric contents after 1 hour, showing that only about 50% of the glucose is absorbed during the test. Also, the curves obtained in giving 2 doses of glucose were quite similar to those seen during the first hour of the standard test. Warren and associates[32] also found the maximal glucose absorption from the gastroduodenal unit in their subjects to be about 43 gm. per hour. These findings have been confirmed by others[17,22], and cast doubt upon the validity of giving 2 doses ½ hour apart. The 1 hour, 2 dose test is therefore subject to the same errors as would be is equivalent to the similar wide scatter seen in the standard test at 1 hour. When our data on the standard and 2 dose tests are analyzed as to the amount of rise or fall in blood sugar level between the ½ hour and the 1 hour specimen very similar values are obtained in the 2 tests. These results appear in Table 3. They demonstrate that the number of cases showing a rise or a fall in sugar level at 1 hour is essentially the same, whether or not 2 doses are given, and lend support to the above observations. Of equal interest is the remarkable equivalence of the 2 hour sugar levels on both

TABLE 3.—DIFFERENCES IN BLOOD SUGAR LEVEL BETWEEN ½ HR. AND 1 HR. SPECIMENS OF STANDARD AND EXTON-ROSE TEST ON SAME INDIVIDUALS

Change in Blood Glucose	*Standard*			*Exton-Rose*		
	No. Cases	*Av. Rise**	*Av. Fall**	*No. Cases*	*Av. Rise**	*Av. Fall**
			Controls			
Rise	18	26		33	25	
Fall	77		28	67		22
No Change	8			3		
	103			103		
			Diabetics			
Rise	22	71		25	73	
Fall	3		61	1		44
No Change	1			0		
	26			26		

*Mg. per 100 cc.

expected in using the peak level of the standard oral test as the critical value. The mean 1 hour level in this group was 132 mg. per 100 cc. with a S.D. of 34 mg. The expected range of the 1 hour value (M + 2 S.D.) would be 64 to 198 mg., and some patients might be expected to range up to 232 mg. (3 S.D.). This is quite similar to the expected range of the 1 dose oral test at the same time interval employing 100 gm. of glucose (Table I). The actual range obtained was 72 to 223 mg. A S.D. of the magnitude of 34.0 units is evidence of a group with considerable scatter about the mean and tests and the general shape of the curves where the 1 hour, 2 dose test is prolonged to 2 hours. A comparison of the mean blood sugar curves of the standard test and those cases in which the 1 hour, 2 dose test was prolonged to 2 hours (Table 1) in our control series demonstrates this similar pattern. This is also evident in comparing the individual curves for the 2 tests. We, therefore, agree with Langner and co-workers that the Exton-Rose (1 hour, 2 dose) test is based upon false assumptions and is essentially the same procedure as the standard test. The criteria for judging normality and ab-

normality are based upon a different, more variable, and less significant portion of the blood sugar curve, namely the height to which the blood sugar level rises. As previously concluded from our observations on the standard test carried out on the control group, the peak of the curve appears to be of little diagnostic value. Therefore, in view of these observations the same conclusions can be drawn for the 1 hour, 2 dose test. It is reasonable that the height of the curve should be greater in the diabetic in whom those homeostatic mechanisms which operate so nicely in the normal individual are disturbed. However, the height attained is probably not so regularly proportional to the degree of disturbance as is the rapidity with which the organism is able to recover normal blood sugar levels.

Summary. 1. Three glucose tolerance tests (3 hour, 1 dose ["standard"]; 1 hour, 2 dose [Exton-Rose]), and intravenous were performed on 103 normal control subjects and 26 clinically diagnosed diabetic patients. Two hour postprandial blood sugar levels were determined following a standard meal in these groups. Of the tests, the "standard" oral test appears to be the most valid, being most specific and sensitive.

2. Both the standard oral and the intravenous tests are satisfactory for clinical use as a diagnostic aid. The intravenous test, because of its somewhat lower sensitivity, might cause mild carbohydrate metabolic disturbance to be missed. Borderline results using this test are, therefore, possibly more indicative of metabolic disturbance than similar results with the standard test. The intravenous test, since it eliminates the influence of gastrointestinal absorption, should be of value in determining carbohydrate tolerance in cases in which absorption defect is suspected.

3. The 3 hour blood sugar level of the standard test is of some value in estimating the severity of the metabolic disturbance in cases showing delayed curves at 2 hours, but is of little diagnostic value *per se*.

4. Results of the tests in 103 control subjects lead us to conclude that a normal 1 dose oral test consists of a fasting blood sugar level of 120 mg. per 100 cc. or less, and a 2 hour level of 125 mg. per 100 cc. (M + 2 S.D.) or less. Two hour blood sugar values above 140 mg. (M + 3 S.D.) should be taken to be diabetic. Values between 125 and 140 mg. should be regarded as presumptively diabetic until proven otherwise. Similarly, a normal intravenous test consists of a normal fasting blood sugar and a 2 hour level of 114 mg. (M + 2 S.D.) or less. Levels above 127 mg. (M + 3 S.D.) should be regarded as diabetic, and between 114 and 127 mg. as presumptively diabetic. The height of the curve is thought to be of no diagnostic significance. These observations parallel observations made on the individual tests throughout the literature by other investigators.

5. The 2 hour postprandial blood sugar level shows fairly good correlation with the standard and intravenous tests, and is a simple means of estimating the ability to utilize carbohydrate, acting as a presumptive test. Two hour blood sugar levels below 134 mg. per 100 cc. (M + 2 S.D.) are regarded as normal, between 134 and 151 mg. as presumptively diabetic, and above 151 mg. (M + 3 S.D.) as frankly diabetic.

6. The diagnostic criteria for the 1 hour, 2 dose test (Exton-Rose) advanced by Matthews and his associates are the most acceptable ones available. The test, however, is overly sensitive, resulting in false diabetic curves in a significant number of normal persons. In addition, it is believed to be based upon false assumptions and should, therefore, be discarded.

7. Where the consideration of simplicity and fewer number of venipunctures arises to recommend the 1 hour, 2 dose test, it is thought that the technique of the standard test with determination of the fasting and 2 hour sugar levels only offers more reliable information.

8. Many conditions result in alterations in glucose tolerance tests, so that they are not specific for diabetes mellitus. As with any clinical test, they must be evaluated in relation to the clinical picture. If this is done, they are of considerable clinical value.

REFERENCES

1. **Bang, I.**: Der Blutzucker. Wiesbaden, 1913.
2. **Benedict, S. R.**: J. Am. Med. Assn., **57,** 1193, 1911.
3. **Conn, J. W.**: Am. J. Med. Sci., **199,** 555, 1940.
4. **Conn, J. W.**, and **Newburgh, L. H.**: Proc. Soc. Exp. Biol. and Med., **36,** 236, 1937.
5. **Cori, C. F.**, and **Cori, G. T.**: Annual Rev. Biochem., **3,** 151, 1934.
6. **Deren, M. D.**: J. Lab. and Clin. Med., **22,** 1138, 1937.
7. **Duncan, G. G.**: Diseases of Metabolism, 2d ed., Philadelphia, W. B. Saunders, 1947.
8. **Exton, W. G.**, and **Rose, A. R.**: Am. J. Clin. Path., **4,** 381, 1934.
9. **Folin, O.**, and **Wu, H.**: J. Biol. Chem., **38,** 81, 1919; **41,** 367, 1920.
10. **Gilbert, M.**, **Schneider, H.**, and **Boch, J. C.**: J. Biol. Chem., **67,** 629, 1926.
11. **Gould, S. E.**, **Altshuler, S. S.**, and **Mellen, H. S.**: Am. J. Med. Sci., **193,** 611, 1937.
12. **Hamman, L.**, and **Hirschman, I. I.**: Arch. Int. Med., **20,** 761, 1917.
13. **Joslin, E. P.**, **Root, H. F.**, **White, P.**, and **Marble, A.**: The Treatment of Diabetes Mellitus, 7th ed., Philadelphia, Lea & Febiger, 1940.
14. **Kelly, H. T.**: Penna. Med. J., **39,** 972, 1936.
15. **Kolmer, J. A.**: Clinical Diagnosis by Laboratory Examinations, Chap. 4, pp. 147-161, New York, D. Appleton-Century, 1944.
16. **Langner, P. H., Jr.**, and **Dewees, E. J.**: Am. J. Med. Sci., **204,** 85, 1942.
17. **Langner, P. H., Jr.**, **Romansky, M. J.**, and **Robin, E. D.**: Am. J. Med. Sci., **212,** 466, 1946.
18. **Lawrence, R. D.**: Med. Clin. N. Am., **31,** 289, 1947.
19. **Lennox, W. G.**: J. Clin. Invest., **4,** 331, 1927.
20. **Leonards, J. R.**, and **Free, A. H.**: J. Lab. and Clin. Med., **30,** 1070, 1945.
21. **Lozner, E. L.**, **Winkler, A. W.**, **Taylor, F. H. L.**, and **Peters, J. P.**: J. Clin. Invest., **20,** 507, 1941.
22. **Matthews, M. W.**, **Magath, T. B.**, and **Berkson, J.**: J. Am. Med. Assn., **113,** 1531, 1939.
23. **Minot, A. S.**: Personal Communications.
24. **Moyer, J. H.**, and **Womack, C. R.**: Am. J. Med. Sci., **216,** 446, 1948.
25. **Newburgh, L. H.**: Ann. Int. Med., **17,** 935, 1942.
26. **Robinson, W. G., Jr.**, **Shelton, P.**, and **Smith, F. V., Jr.**: Arch. Int. Med., **68,** 945, 1941.
27. **Soskin, S.**, and **Allweiss, M. D.**: Am. J. Physiol., **110,** 4, 1934.
28. **Staub, H.**: Ztschr. f. Klin. Med., **91,** 44, 1921; II Mitteilung. Ibid., **93,** 89, 1922.
29. **Thannhauser, S. J.**, and **Pfitzer, H.**: Munch. Med. Woch., **40,** 2155, 1913.
30. **Trimble, H. C.**, **Carey, B. W., Jr.**, and **Maddock, S. J.**: J. Biol. Chem., **100,** 125, 1933.
31. **Tunbridge, R. E.**, and **Allibone, E. C.**: Quart. J. Med., **9,** 11, 1940.
32. **Warren, R.**, **Karr, W. G.**, **Hoffman, O. D.**, and **Abbott, W. O.**: Am. J. Med. Sci., **200,** 639, 1940.
33. **Watson, E. M.**: Canad. Med. Assn. J., **36,** 454, 1937.
34. **Wayburn, E.**, and **Gray, H.**: Am. J. Med. Sci., **204,** 823, 1942.
35. **Wishnofsky, M.**: Arch. Int. Med., **42,** 443, 1928.
36. **Woodyatt, R. T.**: Harvey Lect., **11,** 326, 1915-16.

DIAGNOSTIC VALUE OF HISTOLOGIC LESIONS OF STRIATED MUSCLE IN RHEUMATOID ARTHRITIS*

By Leon Sokoloff, M.D.

Sigmund L. Wilens, M.D.

Joseph J. Bunim, M.D.

AND

Currier McEwen, M.D.

NEW YORK, NEW YORK

(From the Departments of Pathology and Medicine and the Study Group on Rheumatic Diseases, New York University College of Medicine, Laboratories of Pathology, and the Third Medical Division, Bellevue Hospital)

In 1945, a distinctive inflammatory lesion in the striated muscle in rheumatoid arthritis was described by Freund, Steiner and their associates[7]. The lesion, essentially a focal infiltration of lymphocytes and plasma cells, was called "nodular polymyositis." It was found to be widely disseminated throughout the various muscles and could be demonstrated with regularity by biopsy. No similar lesions were found in a large number of unselected control cases. These observations excited considerable interest among rheumatologists in this country and abroad because of the lack of satisfactory diagnostic tests for rheumatoid arthritis, particularly in the early stages of the disease. Further reports by Steiner[15] added support to the concept of the specificity of the lesion. Within a short period of time, the presence of the lesion in the muscle in most cases of rheumatoid arthritis was confirmed by several other observers[6,8,13,16].

That the lesions are not specific for rheumatoid arthritis was suggested by isolated observations of several investigators[2]. Clawson, Noble and Lufkin[4] found them in the deltoid muscle of 4.2% of 450 consecutive necropsies. DeForest and his co-workers[6] saw them in a few patients with non-specific infectious arthritis and osteoarthritis as well as in rheumatoid arthritis. In June, 1948, evidence was presented in a preliminary report[3] that lesions, histologically similar to or identical with those seen in rheumatoid arthritis, may occur in rheumatic fever, osteoarthritis and certain other diseases, and it was concluded that this lesion was therefore not specific. Similar conclusions were drawn by Ogryzlo[14] from a study of the muscle in 158 cases of many different diseases.

It is not without historical interest that Klinge[10], in 1932, reported the presence of similar lesions in striated muscle obtained at necropsy from 2 of 6 patients with rheumatoid arthritis. Unlike the granulomatous nodules he described in rheumatic fever, these were regarded as histologically non-specific. Curtis and Pollard[5], in 1940, observed the infiltrates in rheumatoid arthritis and in Felty's syndrome, and believed they represented another feature common to the 2 diseases. The "lymphorrhages" described in myasthenia gravis by Mandelbaum[11] fre-

* This work was aided by a grant from the J. M. Kaplan Foundation.

quently are compact and resemble the "nodules" of Steiner *et al.*

The present investigations were undertaken in an attempt to evaluate the lesions found in muscle obtained by biopsy as a diagnostic test for rheumatoid arthritis. The procedure differs somewhat from previous studies in certain respects. The control cases were selected in large part from those rheumatic conditions that might at times be confused clinically with rheumatoid arthritis, such as rheumatic fever, osteoarthritis, gout, tuberculous and other types of arthritis. In addition, muscle was obtained from a number of healthy volunteers, and from individuals with other conditions that have certain pathologic relationships to those diseases mentioned above, such as inactive rheumatic heart disease, subacute bacterial endocarditis and pulmonary tuberculosis. Another feature of this study is that serial sections of the muscle were made in each case.

It was deemed necessary to subject the non-rheumatoid biopsies to exactly the same procedures as the rheumatoid ones, especially in respect to serial sectioning. In previous reports, it is not clearly stated that this had been done. It was hoped that this procedure would disclose the incidence and size of the lesions in the muscle and that a determination could be made as to their relative usefulness if not absolute value as an aid in the diagnosis of the arthritis.

Method and Materials. The 202 cases of this series include 57 cases of rheumatoid arthritis in various stages of activity and 10 of Marie-Strümpell spondylitis with and without peripheral rheumatoid arthritis. Another 21 patients had active rheumatic fever with 1 or more of the following manifestations: polyarthritis, valvulitis, carditis or chorea. In addition, there were 11 cases of inactive rheumatic heart disease, 19 of degenerative arthritis (osteoarthritis), 10 of tuberculous spondylitis or arthritis, and 8 of gout. The group of miscellaneous controls included disseminated lupus erythematosus, acute infectious arthritis due to specific organisms, syphilis, glomerulonephritis, asthma and subacute bacterial endocarditis. The clinical study of these cases was planned with a view of elucidation of the factors concerned in the development of these lesions; it included, in addition to clinical, roentgenographic and routine laboratory studies, the appropriate determination of the erythrocyte sedimentation rate, the serum titer of agglutinins for 3 strains of group A hemolytic streptococci, agglutinins for sensitized sheep red cells, the serum titer of antisteptolysin-O, and precipitins for trichinella antigen.

In all but 20 instances, where necropsy was performed, the muscle was obtained by biopsy. As a rule the specimen was taken from the gastrocnemius muscle; in a few cases, from the quadriceps femoris. The necropsy specimen, principally from cases of rheumatic fever and rheumatic heart disease, was most often the psoas muscle with a smaller proportion from the deltoid. The lesions, when present in material obtained at necropsy, were identical with those found in biopsy specimens.

There were 13 healthy adult volunteers. These had no history or physical signs of any of the rheumatic diseases. The electrocardiogram, roentgenograms of the chest, erythrocyte sedimentation rate, blood Wassermann reaction, and the serum titer of streptococcus agglutinins, sensitized sheep red cell agglutinins, and precipitins for trichinella antigen were all normal.

The most satisfactory method of fixation was found to be immersion of the excised muscle in 10% formalin for ½ to 1 hour; then washing in tap water for ½ to 1 hour; finally completing the fixation in Zenker's solution without the addition of acetic acid or formalin. In each instance, approximately 400 serial sections were cut. The average area of the stained section was 1 centimeter squared, and the thickness, 8 micra. Every fifth section was stained with hematoxylin and eosin. In certain instances, sections were also stained for elastic tissue (Weigert's stain), for reticulum (Wilder's stain) and fibrin (Brown-Breen's stain). The average unit volume of muscle studied, after fixation and staining, was 0.32 cc. More than 80,000 sections were cut, and of these, over 17,000 were stained and examined. The number of cells in the individual lesions was counted, as well as the number of lesions in the unit volume of muscle. The area of the smallest and largest lesions in each case was measured with an eyepiece micrometer. The mean diameter was then calculated as if this were the area of a circle.

In addition to the histological study, chemical analysis of the muscle of 40 of these cases was also performed and the results will be reported elsewhere by Bien, Ziff, Bunim and McEwen[1].

Criteria for Diagnosis. Because of the frequency of mild inflammatory and degenerative changes in striated muscle, it is necessary to define precise criteria for the diagnosis of the so-called muscle "nodule." The criteria used in this series, although arbitrarily selected, incorporate those of Steiner[15] with certain quantitative limits not previously described.

1. *Cell type.* The predominant cell is the lymphocyte. There is a much smaller proportion of sarcolemmal nuclei, plasma cells, mast cells, endothelial and mononuclear cells and polymorphonuclear leukocytes. Cells resembling fibroblasts or epithelioid cells may rarely be present, but are never more than 5% of the total.

2. *Compactness.* The cell aggregate must be compact and the distance intervening between the great majority of the cells be no greater than the diameter of the average cell.

3. *Framework.* There is a small amount of preformed collagen and occasionally of adipose tissue in the inflammatory focus, but no reticulum. The presence or absence of reticulum was determined by Wilder's method.

4. *Number of cells.* Because minute foci of cellular infiltrations are commonly found throughout our series, 50 cells in a single lesion is the minimal number accepted.

5. *Size.* The minimal limit of the size of the acceptable lesion is a mean diameter of 35 micra. In a few instances, the lesion was sectioned at a longitudinal tangent to a blood vessel and thus appeared long but narrow. The minimal acceptable width of such an accumulation is 35 micra.

6. *Contour.* The lesion may have any configuration. This is determined largely by the location of the cell aggregate. Within the endomysium, its margins are necessarily linear because of its relations to adjacent muscle fibers. In this position, it may infiltrate for a short distance between adjacent muscle fibers, and the shape therefore becomes stellate. If the distribution is in relation to a blood vessel, the cells form a complete or incomplete collar. In adipose tissue, the contours are often less regular than elsewhere because of the intervening fat cells.

7. *Circumscription.* No matter what the configuration, the lesion is essentially circumscribed ("nodular") and not diffuse as in certain other types of myositis.

8. *Location.* The lesions may be located in the endomysium, perimysium or epimysium. They may or may not be related to the nerves or vessels in these locations. The vessels may be arteries, veins or capillaries. In some instances, the cells involve the adventitia but not the media or intima of the vessel.

9. *Necrosis.* The inflammatory foci do not contain fibrin, erythrocytes or blood pigment. There is no fibrinoid change in the collagen such as is seen in the subcutaneous nodule of rheumatoid arthritis. While secondary degenerative changes may take place in the adjacent muscle fibers, there is no necrosis of the inflammatory cells.

Results. The results have been divided into 4 categories: *Positive*, *doubtful*, *negative* and *atypical*. A large number of cases have a focal chronic inflammatory reaction, similar in some respects to the acceptable lesions, but lacking in certain of the specified requirements. Most of the lesions not included were unacceptable because of their small size. In others the proportion of lymphocytes was too small. These are classified as *doubtful*. The last group, labelled *atypical*, consists of focal chronic in-

flammatory reactions with qualitatively different features. There were 9 such cases in this series. Three of these were of lesions of active trichinosis; 3 had the morphologic character of miliary tubercles: 2 others resembled the granulomata of erythema nodosum[12]. The ninth had an unclassified granulomatous character with many multinucleated giant cells and involvement of walls of blood vessels as well as muscle. These data are summarized in Table 1.

Of the cases of Marie-Strümpell ankylosing spondylitis 40% had positive lesions. This differs from the uniformly negative results of the English observers[8], and is most likely attributable to the larger number of sections made from each specimen of the present series.

In the non-rheumatoid group, acceptable lesions were found in a large proportion of the cases of active rheumatic fever, though not in inactive rheumatic heart disease. Positive lesions were obtained also in a goodly proportion of the cases of gout, degenerative arthritis, infectious arthritis and subacute bacterial endocarditis. Furthermore 3 of the 13 healthy adult volunteers had lesions that met the diagnostic criteria in every respect.

TABLE 1. HISTOLOGICAL FINDINGS IN 202 MUSCLES

Disease	Total	Positive	Doubtful	Negative	Atypical
Rheumatoid arthritis	57	32	8	17	0
Ankylosing spondylitis	10	4	2	3	1
Rheumatic fever, active	21	7	4	10	0
Rheumatic heart disease, inactive	11	0	3	8	0
Osteoarthritis	19	4	4	11	0
Joint tuberculosis	10	3	0	6	1
Pulmonary tuberculosis	6	0	1	3	2
Gout	8	3	3	2	0
Subacute bacterial endocarditis	6	4	1	1	0
Trichinosis	3	..	..	..	3
Miscellaneous*	38	8	10	18	2
Normal	13	3	3	7	0
Total	202	68	39	86	9
Percent of 57 rheumatoid	100	56	14	30	0
Percent of 145 non-rheumatoid	100	25	21	48	6

* The 38 miscellaneous diseases consisted of 6 cases of pyogenic arthritis caused by specific organisms, 2 of non-specific infections arthritis, 6 of syphilis, 6 of neurological disease, 4 of asthma, 3 of glomerulonephritis, 3 of erythema nodosa, 2 of lupus erythematosus, 2 of pneumococcus bacteremia and one each of Boeck's sarcoid, Baker's cyst, infectious mononucleosis and Paget's disease.

To allow comparison with previously reported series, ankylosing spondylitis was classified separately from cases of rheumatoid arthritis. There were 57 cases of rheumatoid arthritis including 4 of Still's disease. Of these, 32 (56%) had positive lesions. This incidence compares closely with the 59% of Desmarais[8] and the 57% of Morrison and his co-workers[13]; it is considerably higher than the 39% of Wells and Wetherby[16] and the 25% of Ogryzlo[14], but much less than the 82% of DeForest[6] and the 96% of Steiner and Chason[15].

All in all, 25% of the non-rheumatoid control cases had the lesions. If the controls are divided into 2 groups, those with the rheumatic diseases and those without them (such as neurological disease with muscle atrophy, syphilis, bacterial endocarditis, asthma, nephritis and the normal persons), the

incidence of positive lesions rises to 30% in the former and falls to 20% in the latter. The character of the control material explains in part the difference in the results of this series from some of the others.

The difference between the rheumatic and non-rheumatic controls is accentuated by considering the incidence of the lesions within the unit volume of muscle (0.32 cc.). Fig. 1 represents the number of "nodules" in this amount of muscle in the 3 groups of cases. As will be noted, approximately 43% of the rheumatoid cases had 5 or more lesions. In the cases of rheumatic diseases other than rheumatoid arthritis a somewhat smaller proportion (20%) had 5 or more infiltrates, but in the non-rheumatic group there were only a few lesions in each case. It is for this reason that a casual section of muscle is less likely to reveal the presence of the lesion in the non-rheumatic group than in the other two.

A further attempt to distinguish the lesions of rheumatoid arthritis from those of the other groups was made on

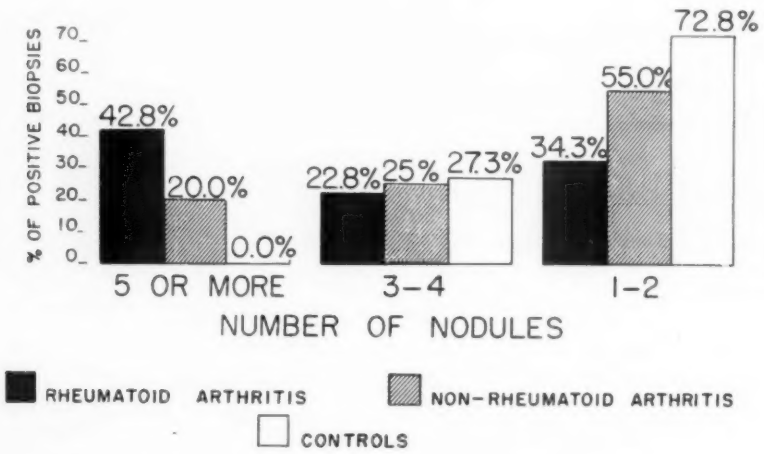


FIG. 1. Number of nodules per unit volume of muscle in positive cases.

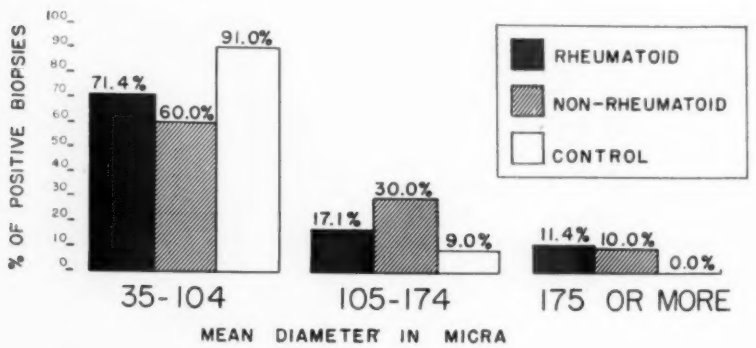


FIG. 2. Mean diameter of largest nodule in positive muscle biopsies from 35 rheumatoid arthritis, 20 non-rheumatoid arthritis and 11 control patients.

the basis of the size of the inflammatory focus (Fig. 2). They were divided into 3 groups according to the mean diameter of the largest lesion in each case: 35 to 104 micra, 105 to 174 micra and 175 micra and greater. Although it is true that very large lesions have not been seen in the non-arthritic controls, no important difference can be made out between the rheumatoid and the other rheumatic cases on this basis.

FIG. 3. An example of the largest type of lesion in the present series. Specimen taken from vastus lateralis from a 34 year old colored woman with rheumatoid arthritis of 10 years' duration. This endomysial lesion has approximately 1500 cells; mean diameter, 400 micra. Isolated muscle fibers are choked off with secondary change, including hyalinization, atrophy and mild basophilia. The remainder of the muscle fibers are within normal limits (x 192).

The same is true if the number of cells in the lesions is considered; this determines the size of the inflammatory foci.

Atrophy of muscle with isolated areas of basophilic or vacuolar degeneration of sarcoplasm was seen in many groups but this had no distinctive pattern in the cases of rheumatoid arthritis; nor was this necessarily associated with the lesion.

Most of the lesions were located in the endomysium although a fair proportion were in the perimysium and occasionally in the epimysium. No distinction could be made among the various groups because of the location.

The perineurium of the nerves of the muscles was not involved in any cases of rheumatoid arthritis, but this was seen in one case of rheumatic fever.

Focal arteritis, resembling in certain respects periarteritis nodosa and the coronary arterial lesions of rheumatoid arthritis, described by Graef[9], was present in 4 cases of rheumatoid arthritis. It also occurred in 1 of 2 cases of disseminated lupus erythema-

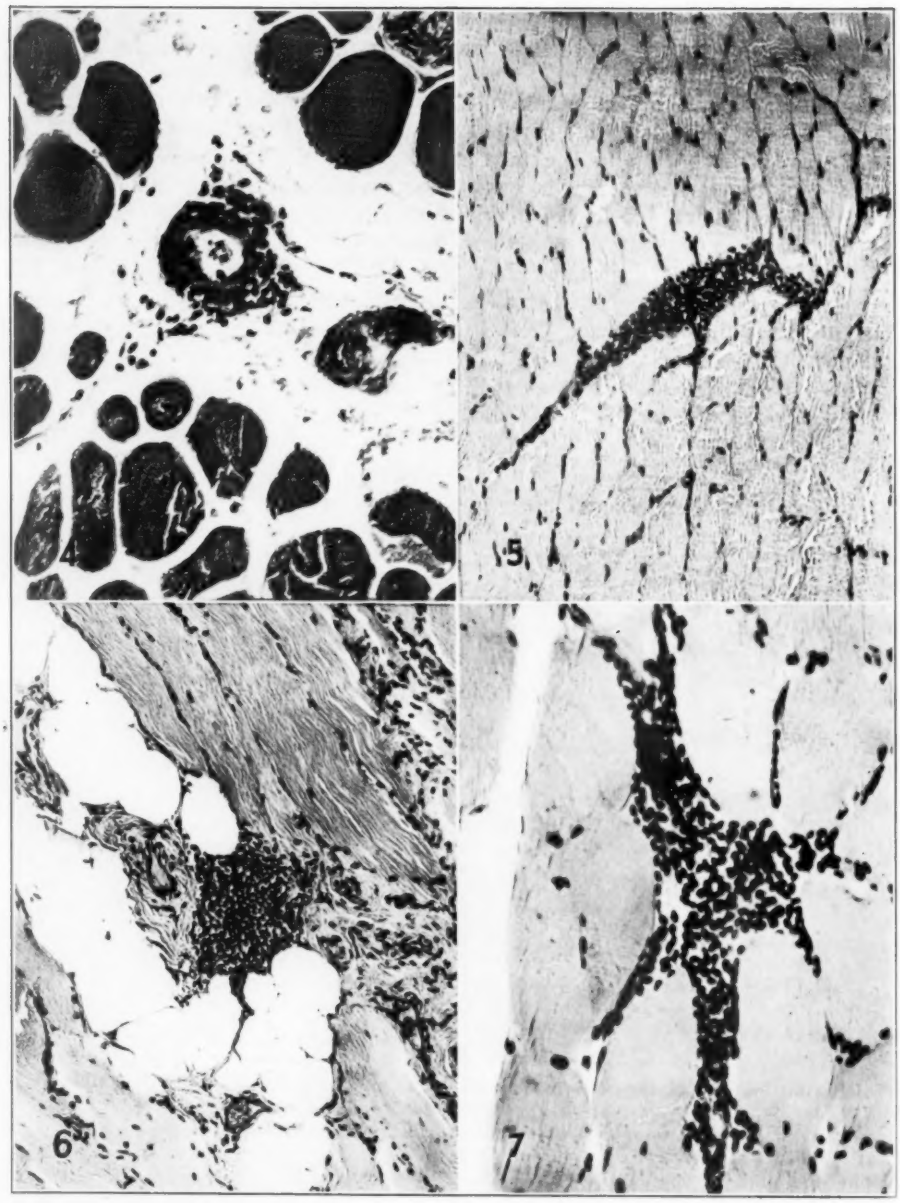


FIG. 4. The smallest acceptable lesion. A perivascular collar of some 50 cells, principally lymphocytes. The muscle fibers reveal a mild degree of atrophy. The patient has had rheumatoid arthritis involving upper and lower extremities for 13 years (x 288).

FIG. 5. A lesion in the vastus lateralis of a 13 year old girl with active rheumatic carditis and rheumatic polyarthritis of 3 months' duration. No atrophy of the muscle. The "nodule" has approximately 310 cells, principally lymphocytes, and its mean diameter is 116 micra (x 192).

FIG. 6. This "nodule" is one of many found in the gastrocnemius of a 74 year old Negro with all the classic clinical and roentgenographic characteristics of gout. The serum uric acid at the time of biopsy was 7.4 mg. %. The lesion is located in the perimysial margin of a muscle bundle and lies next to an arteriole. There are 370 lymphocytes and the mean diameter is 110 micra (x 192).

FIG. 7. An endomysial lesion in the gastrocnemius of an apparently healthy volunteer. He is a 31 year old white man, a hospital attendant, with no evidence of present or past rheumatic disease. There are more than 200 lymphocytes in the infiltrate and this is regarded as an acceptable lesion in every respect (x 360).

tosus and 1 of rheumatic heart disease with multiple arterial thrombi.

Active lesions of trichinosis were present in 3 cases and isolated cysts, without inflammatory reaction, were seen in 3 others.

Discussion. Analysis of the clinical and laboratory data of the patients with rheumatoid arthritis fails to elucidate the factors that are responsible for the development of the lesion. Neither the incidence nor the severity of the muscle lesion appears to bear any relationship to the distribution of joint involvement; severity or activity of the arthritis, as reflected by the symptoms of pain, periarticular swelling and stiffness or by the erythrocyte sedimentation rate; the progress of the disease or the response to gold therapy. In general, the lesions were not more frequent in patients with marked atrophy of the muscle than in those without it. There was no correlation with the age of the patient, the sex, or the duration of the illness. In some instances, lesions were found 5 months following the onset of the symptoms of rheumatoid arthritis, and in others they were lacking even when the disease had been present for 30 years. There was no relationship between the presence or absence of lesions and the serum titer of agglutinins for group A hemolytic streptococci and sensitized sheep red cells. Patients with subcutaneous nodules are not more likely to have muscle lesions than those without them. The proportion of patients treated with gold was the same in the negative and positive groups of rheumatoid cases.

In the non-rheumatoid as well as the rheumatoid group, the lesion could be found in the gastrocnemius even when the arthritis involved some distant joint. The lesion occurred without any significant titer of precipitins for trichinella antigen.

It has not been possible to trace the life history of the lesions. It is not known how soon they appear, how long they persist, or if they disappear. That they may disappear in rheumatic fever is strongly suggested by their absence in the group of cases of inactive rheumatic heart disease compared with the relatively high incidence in active rheumatic fever. On the other hand, they occur frequently in the rheumatoid group long after other evidences of activity have subsided. In no instance has there been any evidence that they heal with scar formation.

The chemical analysis of the muscle in 39 of the cases[1] demonstrates that along with atrophy of the muscle, there occurs a fall in its total protein content. This fall is attributable, in a large degree, to a decrease of the myosin fraction of the muscle protein. Moreover, this change is accompanied by a diminution of the adenosine-triphosphatase activity of the myosin present. There is no increase of the collagen component of the muscle protein to replace the loss of myosin. Of the muscle specimens obtained from normal volunteers, those containing cellular infiltrates without atrophy showed a significant diminution of the myosin content compared to the specimens that were free of infiltrates.

It is believed that the lesions described here are not specific for rheumatoid arthritis. Furthermore, their occurrence in rheumatic disease other than rheumatoid arthritis is not sufficiently less frequent to permit the use of the muscle biopsy as a satisfactory diagnostic test for rheumatoid arthritis.

Summary. Serial sections of striated muscle, obtained principally by biopsy, were studied in 202 cases of rheumatoid arthritis, other rheumatic diseases (including rheumatic fever, osteoarthritis, gout and infectious arthritis), various non-rheumatic diseases

and healthy individuals. The lesions described by Freund and Steiner have been found in 56% of patients who had rheumatoid arthritis. Lesions similar to or indistinguishable from these were found in many other rheumatic and non-rheumatic states, although in lesser incidence. They were also present in 3 of 13 healthy volunteers. It is concluded that the muscle biopsy is of little value as a diagnostic procedure for rheumatoid arthritis.

REFERENCES

1. **Bien, E., Ziff, M., Bunim, J. J.,** and **McEwen, C.**: To be published.
2. **Black-Schaffer, B.,** Discussion of Steiner *et al.*: Am. J. Path., **22**, 647, 1946.
3. **Bunim, J. J., Sokoloff, L., Wilens, S. L.,** and **McEwen, C.**: Proc. Am. Rheum. Assn., June 19, 1948. Abst. Ann. Rheum. Dis., **7**, 251, 1948.
4. **Clawson, B. J., Noble, J. F.,** and **Lufkin, N. H.**: Arch. Path., **43**, 579, 1947.
5. **Curtis, A. C.,** and **Pollard, H. M.**: Ann. Int. Med., **13**, 2265, 1940.
6. **DeForest, G. K., Bunting, H.,** and **Kenney, W. E.**: Am. J. Med., **2**, 40, 1947.

7a. **Freund, H. A., Steiner, G., Leichtentritt, B.,** and **Price, A. E.**: Science, **101**, 202, 1945.

7b. **Steiner, G., Freund, H. A., Leichtentritt, B.,** and **Price, A. E.**: Am. J. Path., **22**, 103, 1946.

8a. **Gibson, H. J., Kersley, G. D.,** and **Desmarais, M. H. L.**: Ann. Rheum. Dis., **5**, 131, 1946.

8b. **Desmarais, M. H. L., Gibson, H. J.,** and **Kersley, G. D.**: Ann. Rheum. Dis., **7**, 132, 1948.

9. **Graef, I., Hickey, D.,** and **Altman, V.**: Cardiac lesions in rheumatoid arthritis. To be published.
10. **Klinge, F.,** and **Grzimek, N.**: Virch. Arch. f. Path. u. Path. Anat., **284**, 646, 1932.
11. **Mandelbaum, F. S.**: J. Exp. Med., **10**, 308, 1908.
12. **Miescher, G.**: Acta Derm.-Venereol., **27**, 447, 1948.
13. **Morrison, L. R., Short, C. L., Ludwig, A. O.,** and **Schwab, R. S.**: Am. J. Med. Sci., **214**, 33, 1947.
14. **Ogryzlo, M. A.**: Arch. Path., **46**, 301, 1948.
15. **Steiner, G.,** and **Chason, J. L.**: J. Lab. and Clin. Med., **18**, 931, 1948.
16. **Wells, S. M.,** and **Wetherby, M.**: Cited by Clawson *et al.*[4].

THE ROLE OF LIPID DEPOSITION IN RENAL ARTERIOLAR SCLEROSIS

By S. L. Wilens, M.D.

AND

S. K. Elster, M.D.

NEW YORK, NEW YORK

(From the Departments of Pathology, Bellevue Hospital and New York University College of Medicine)

The lesions of arteriolar sclerosis differ in so many ways from those of arterial atherosclerosis that there would appear to be little reason to regard the two as resulting from the same underlying fault. Arteriolar sclerosis is much more intimately related to hypertension than is atherosclerosis. In the absence of hypertension only the follicular arterioles of the spleen regularly undergo hyalinization and thickening, but severe widespread atherosclerosis may develop in persons with normal arterial blood pressures. Arteriolar sclerosis is less directly related to age than is arterial atherosclerosis. Severe arteriolar lesions may be present in young hypertensive persons. They do not increase in incidence as uniformly or progressively with advancing age as do the intimal lesions of larger arteries. No connection between arteriolar sclerosis and hyperlipemia has been demonstrated. Hyperlipemic states are believed to promote the formation of atheromatous plaques.

The lesions of arteriolar sclerosis have a strikingly different distribution from those of atherosclerosis. Although in hypertension the arterioles throughout the body may show medial muscular hypertrophy and concentric intimal proliferation, only those in the splanchnic area, namely in the spleen, pancreas, adrenals, kidneys, liver and intestine, commonly show the more striking lesion of hyalinization or necrosis. The larger arteries of these viscera are not often the seat of advanced atherosclerosis. On the other hand, in some organs such as the heart and brain in which the main arteries frequently become sclerotic, the arterioles seldom show severe sclerotic change of the hyaline type.

The morphology of the 2 types of lesions is strikingly different. Atherosclerosis is primarily intimal in location, whereas in arteriolar sclerosis the media is most profoundly altered. The lesions of arteriolar sclerosis seldom contain lipophages, cholesterol crystals or anisotropic lipid. They almost never undergo calcification. On the other hand, nothing equivalent to the "fibrinoid" necrosis or the acute inflammatory reaction that are sometimes striking in arteriolar sclerosis occur in atherosclerosis.

Yet in spite of these many dissimilarities, there is one feature that is alike in arteriolar and atherosclerosis. The lesions of both commonly contain conspicuous deposits of lipid. Lipid deposition has been regarded by most of arteriolar sclerosis. Fuller[2], however, of arteriolar sclerosis. Fuller[3], however, was so impressed by deposits of lipid in the walls of sclerotic renal arterioles that he stated that arteriolar sclerosis should be regarded as a form of atherosclerosis. Lipid deposition in the intima of arteries has come to be regarded by many as an early and essential feature of the atherosclerotic process. There is no reason to exclude the possibility

that lipid deposition may play a similar role in the lesions of arteriolar sclerosis.

It was with this possibility in view that the present study of arteriolar lipidosis was undertaken. It was decided to study in detail the incidence of lipid deposition in the arterioles of the kidney and the factors that might modify its occurrence. This organ was selected because its arterioles are frequently altered in hypertension. For purposes of comparison a less extensive study of arteriolar lipidosis in other organs was also made.

Materials and Methods. Frozen sections of formalin-fixed kidney tissue stained for fat with Sudan IV were examined from 140 necropsies performed at Bellevue Hospital, New York. These were so selected that the influence of age, sex, race, blood pressure, diabetic hyperlipemia and renal disease on the incidence and severity of renal arteriolar lipidosis might be tested. The distribution of cases among these various categories is revealed in detail in the tables.

All arterioles encountered in cross, oblique, or, more rarely, longitudinal section in consecutive microscopic fields of renal cortex were grouped into 1, those that contained any stainable fat and 2, those that did not. Only extraglomerular vessels with an estimated diameter of less than 100 micra were included. The majority of these consisted of afferent glomerular arterioles. More than 100 arterioles were counted in sections of each kidney.

The number of arterioles encountered in a given area of cortex varied considerably in different types of renal lesions. In normal kidneys, 3 frozen sections with an estimated renal cortex of about 5 sq. cm. were required in order to find 100 arterioles. In arteriolar nephrosclerosis as many as 200 arterioles were detected in a single sq. cm. of cortical tissue. This apparent increase can not be attributed wholly to a loss of intervening cortical parenchyma, since in many such cases more than 50% of the cortical tissue was still preserved. The obvious reason, therefore, for the apparent increase of the number of arterioles in a given area of cortical tissue, in such conditions as arteriolar nephrosclerosis, must be increased length and tortuosity of the original vessels. It was estimated roughly that in this condition, the afferent glomerular arterioles were often 5 times as long as in normal kidneys. This increase of arteriolar length detracts somewhat from the accuracy of differential counting, since, obviously, a single vessel is often encountered several times in cross section. The method, therefore, does not give accurate information as to the actual number of arterioles that contain fat, but does provide a measure of the amount of fat found in the arteriolar system as a whole.

In addition to determining the percentage of fat containing arterioles seen in transverse section, an estimate as to the average amount of fat per arteriole was made. In general, when a high percentage of arterioles in a section contained fat, the fat content of each arteriole was relatively large, but this was not invariably the case. In 6 of 47 kidneys in which the average arteriole that contained fat did so in moderate amounts, more than 50% of the arterioles seen in cross section contained no fat at all. On the other hand, in 13 of 74 kidneys in which more than 50% of all arterioles observed contained some fat, the average amount of fat in these arterioles was considered to be relatively slight. For this reason both types of determinations are included in the Tables.

Similar measurements of arteriolar lipidosis were made on the heart, spleen, pancreas and adrenal of 10 persons with severe protracted hypertension and of 10 persons with normal blood pressure. In the former group the hypertension was known to have lasted, in each instance, for more than 3 years and to have exceeded 175/100 mm. of Hg. in all recorded blood pressure measurements; in each, the heart weight at necropsy was greater than 450 gm. In the latter group, the blood pressure, in each instance, was less than 135/85 and the heart weight less than 350 gm. The prostate, testis, uterus, ovary, diaphragm and brain were examined, when available. The age at death of this group of 20 varied from 39 to 63 years.

Results. Some lipid material was found deposited in the walls of arterioles in 133 (95%) of the 140 kidneys examined. Of the 7 kidneys without any arteriolar lipid, 4 were from infants less than 2½ years of age, 1 was from an 11-year old child, and 2 were from adults in the 6th and 7th decades. In 128 of the 140 kidneys, more than 10% of the arterioles examined contained some lipid. In 17 kidneys considered to be normal from adults, none of whom had had either hypertension or dia-

betes, 15 contained considerable amounts of arteriolar lipid. It may, therefore, be concluded that it is the rule rather than the exception to find some lipid deposited in the walls of the renal arterioles. Such deposition may be considered almost physiological in adults. The alternative explanation is that almost all conditions that lead to death from natural causes may lead to lipid deposition in arteriolar walls.

There was an extreme variation in the amount of arteriolar lipid found under different circumstances. In 6 kidneys, more than 90% of the arterioles contained lipid. In 12, the average amount of lipid found in individual arterioles was very large; in 45, it was moderate and in 76, it was scanty. In general, the amount of lipid found depended on the condition of the arteriolar wall. Arterioles that appeared otherwise normal, usually contained only minute amounts. Arterioles that were thickened or hyalinized, generally, but not invariably, contained large amounts.

The lipid most often seemed to impregnate the media of the vessel; it almost never appeared as rounded spheres or globules of free fat. Occasionally, small pockets of free lipid were lodged between the intima and media. This was seen only in the presence of severe arteriolar sclerosis. In relatively normal arterioles the stainable fat was most usually in the form of thin streaks of rather faintly staining lipid material, obviously impregnating and combined with the tissue of the arteriolar wall.

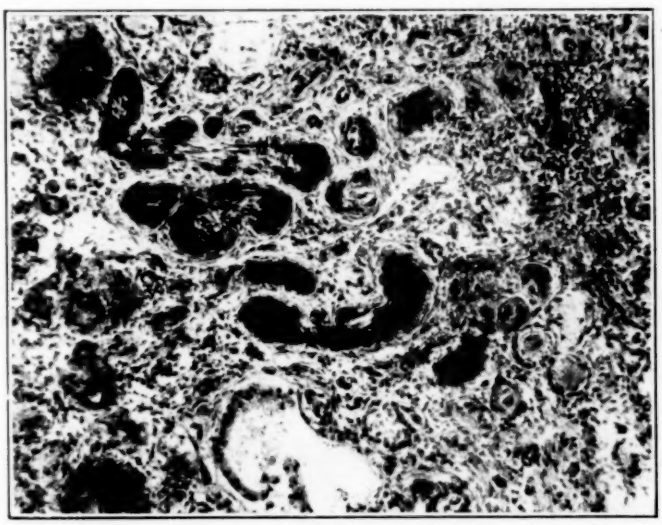


FIG. 1. A group of sclerotic renal arterioles heavily laden with lipid. Frozen section, Sudan IV stain (x 136).

Such delicate deposits had no constant position, and quite often were situated near the external margin of the media. In severe arteriolar sclerosis the arteriolar walls were frequently completely inundated with lipid. Where arterioles were sectioned in the longitudinal plane or as they emerged directly at right angles from the wall of much larger arteries, it was noted that there was a very definite tendency for the lipid deposits to accumulate at the margins of such branch orifices. This localization reproduced in striking miniature

fashion the localization of atheromatous patches at the mouths of arterial branches. This, however, was almost the only resemblance in the morphology of the 2 fat containing lesions. Almost none of the lipid was doubly refractive with polarized light. The emergence of renal cortical arterioles

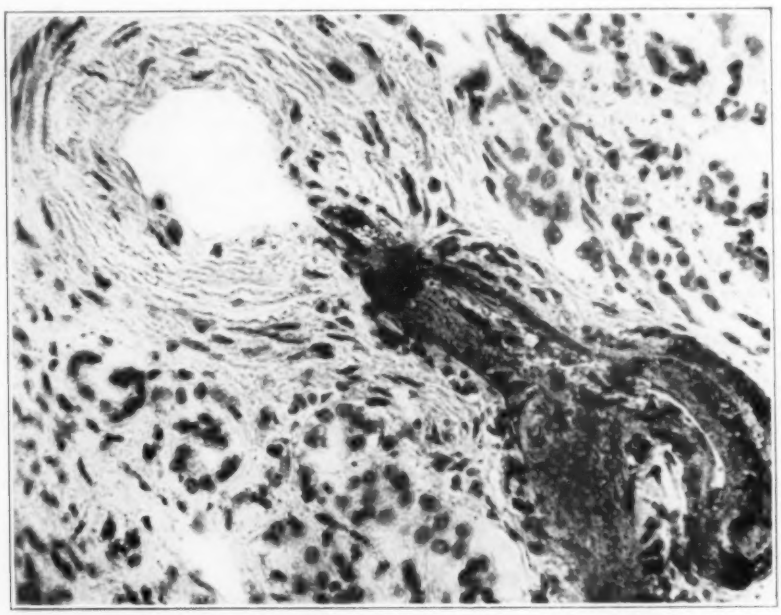


FIG. 2. Heavy lipid deposit in renal arteriole beginning at its point of origin from an interlobular artery. Frozen section, Sudan IV stain (x 414).

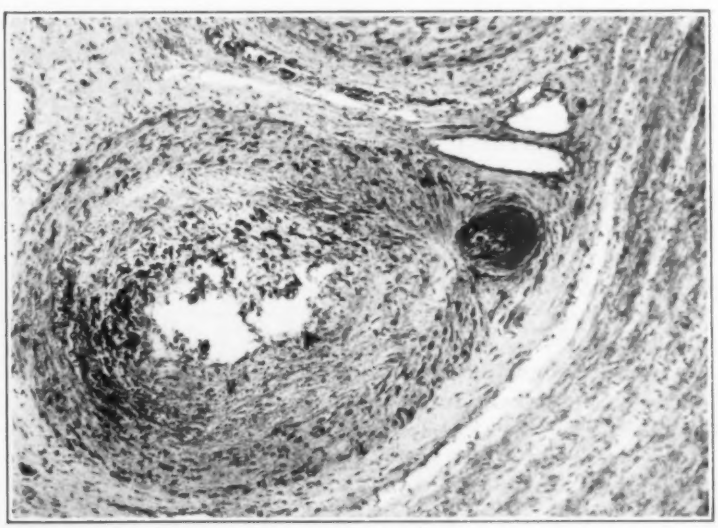


FIG. 3. Lipid deposits in the wall of an arteriole at its point of origin from a large arcuate artery in the kidney. Frozen section, Sudan IV stain (x 108).

by abrupt transition from large interlobular arteries is in striking contrast with many other organs in which arterioles result as a graded series of bifurcations. This anatomical peculiarity at least suggests that renal arteriolar pressure ranges may differ from those of other organs.

Arteriolar lipid deposition appeared to be independent of lipid deposition in any other renal structure. It was often marked when none was found in the glomeruli, tubules or interstitial tissue. In some instances, it was inconspicuous when tubular or interstitial lipid deposits were pronounced. The glomeruli, however, seldom contained much lipid unless the arterioles did also.

TABLE 1. INFLUENCE OF AGE AND SEX ON INCIDENCE OF RENAL ARTERIOLAR LIPIDOSIS

Age	Sex	Number of Cases	Per Cent Arterioles With Lipid Mean	Average Amount of Lipid per Arteriole Marked	Moderate	Slight	None
Less than 30	Men	6	10.2	0	0	3	3
	Women	6	20.3	0	0	4	2
30 – 39	Men	6	22.9	0	1	5	0
	Women	6	48.8	0	2	4	0
40 – 49	Men	10	30.5	0	1	9	0
	Women	11	54.2	2	5	4	0
50 – 59	Men	22	42.8	1	11	9	1
	Women	15	55.5	1	5	9	0
60 – 69	Men	21	42.1	2	7	11	1
	Women	13	63.0	1	5	7	0
70 and over	Men	13	59.4	3	6	4	0
	Women	11	51.4	2	2	7	0
TOTAL	Men	78	39.1	6 (7.7%)	26 (33.3%)	41 (52.6%)	5 (6.4%)
	Women	62	52.9	6 (9.6%)	19 (30.7%)	35 (56.5%)	2 (3.2%)

INFLUENCE OF AGE, SEX AND RACE ON THE INCIDENCE OF RENAL ARTERIOLAR LIPIDOSIS. In Table 1, when both hypertensive and non-hypertensive persons are grouped together, it may be seen that in women over the age of 30 there is no significant change in the incidence of renal arteriolar lipidosis in successive age groups. In men there is a progressive increase until the age of 50, but no constant increase thereafter. Although rather small groups of young persons are included in the series, these are sufficient to indicate that lipid deposition is relatively slight in persons of both sexes before the age of 30. This may be due largely to the infrequency of hypertension in young persons, but of 3 persons under 20 years of age with chronic glomerulonephritis and secondary hypertension, one had no arterioles with lipid and the other 2 had 23.9% and 36.9% respectively. In both these latter kidneys, only slight amounts of lipid were found in individual arterioles.

In the group of 52 that had had normal blood pressures during life and normal-sized hearts at necropsy, a consistent although slight increase of the incidence of renal arteriolar lipidosis is disclosed with each successive decade (Table 2). This increase is so uniform that when plotted (Fig. 4), a straight line is obtained. On the other hand, in the group of 88 that had either hypertension or a hypertrophied heart the incidence of renal arteriolar lipidosis rises abruptly in the age

group 30 to 39 years and does not increase significantly in the succeeding age groups (Table 2 and Fig. 4).

It may be noted (Table 1) that a consistently larger amount of arteriolar lipid was found in women than in men in all but the very oldest age group. This was due only in part to the inclusion of larger proportions of women than of men with diabetes or hypertension. In 30 women with diabetes, 60.0% of the arterioles contained fat; whereas in 28 diabetic men, only 52.2% were similarly involved. In 32 non-diabetic women, 44.6% of the arterioles contained lipid; while in 50 non-diabetic men, the incidence was only 32.5%. Similarly, in 43 women with either hypertension or cardiac hypertrophy, the incidence of renal arteriolar lipidosis was 62.9%; in a similar group of 45 men it was 46.2%. Only in the

TABLE 2. INFLUENCE OF AGE ON THE INCIDENCE OF RENAL ARTERIOLAR LIPIDOSIS IN NON-HYPERTENSIVE AND HYPERTENSIVE SUBJECTS

Age	Without Hypertension or Cardiac Hypertrophy		With Hypertension or Cardiac Hypertrophy	
	Number of Cases	Per Cent Arterioles With Lipid Mean	Number of Cases	Per Cent Arterioles With Lipid Mean
Less than 30	9	13.3	3	30.4
30 – 39	15	20.9	7	46.7
40 – 49	7	27.5	14	52.3
50 – 59	11	32.6	26	54.6
60 – 69	11	39.0	23	52.9
70 and over	9	44.3	15	63.9
TOTAL	52	29.8	88	54.1

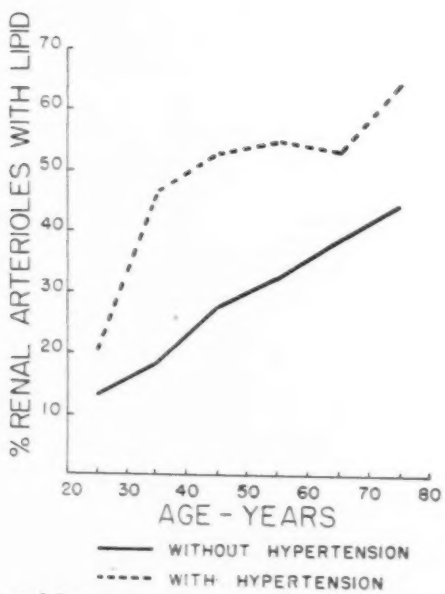


FIG. 4. Relation of age and hypertension to the incidence of renal arteriolar lipidosis. The incidence increases at a uniform rate with advancing age in non-hypertensive persons. The incidence of arteriolar lipidosis in hypertensive persons is consistently higher than in non-hypertensive persons of the corresponding age group but does not increase uniformly with advancing age.

groups with neither hypertension nor cardiac hypertrophy was there no appreciable difference in sex incidence of renal arteriolar lipidosis. In 19 women of this group, the incidence was 27.9% and in 33 men it was 31.9%.

These findings suggest that renal arteriolar lipidosis resembles arterial atherosclerosis in that it is uncommon before the age of 30 to 40 years, and in that its incidence increases consistently and progressively in non-hypertensive persons with advancing age. It is unlike atherosclerosis in that women tend to show a higher incidence than men. The reverse is generally the case in atherosclerosis.

No racial predisposition to develop renal arteriolar deposits of lipid was found. In 118 white persons, the incidence was 45.4%; in 22 negroes, it was 42.0%.

THE RELATION OF HYPERTENSION TO RENAL ARTERIOLAR LIPIDOSIS. When both hypertension (blood pressure over 150/90 mm. Hg.) and cardiac hypertrophy (heart weight over 360 gm. in women and 400 gm. in men) were present, the incidence of renal arteriolar lipidosis was twice as great as when both were absent (Table 3). This difference is statistically significant, as the differences between the means is 7.2 times the standard errors of this difference. It is apparent from percentage distribution curves (Fig. 5)

TABLE 3. RELATION OF HYPERTENSION AND CARDIAC HYPERTROPHY TO RENAL ARTERIOLAR LIPIDOSIS

Hypertension	Cardiac Hypertrophy	Number Cases	Per Cent Arterioles Mean	Average Amount of Lipid per Arteriole With Lipid: Marked	Moderate	Slight	None
Yes	Yes	49	62.6	9	21	19	0
			± 3.2	(18.4%)	(42.8%)	(38.8%)	
Yes	No	9	48.7	0	5	4	0
No	Yes	30	41.9	2	9	17	2
No	No	52	29.8	1	10	36	5
			± 3.2	(1.9%)	(19.3%)	(69.2%)	(9.6%)
TOTAL		140	44.9	12	45	76	7

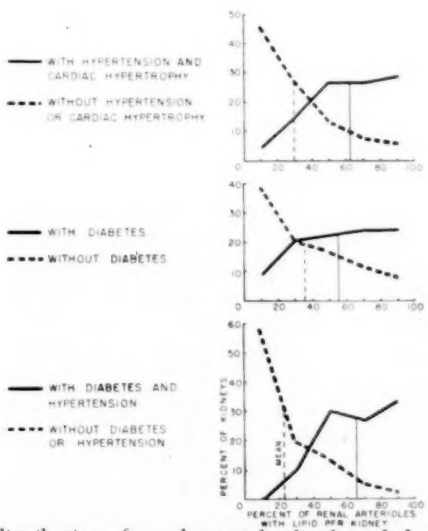


FIG. 5. Percentage distribution of renal arteriolar lipid in diabetes and hypertension.

that in the majority of non-hypertensive cases with normal sized hearts there was a low incidence and in the majority of hypertensive ones with cardiac hypertrophy there was a high incidence of arteriolar lipidosis. It may also be noted (Table 3) that the arterioles were comparatively heavily laden with lipid when both hypertension and cardiac hypertrophy were present. Almost two-thirds of the arterioles in this group were estimated to have either heavy or moderate deposits of fat. Less than one-fourth of the fat-containing arterioles from the kidneys of persons who had neither hypertension nor cardiac hypertrophy had equal amounts of lipid.

THE RELATION OF RENAL DISEASE TO RENAL ARTERIOLAR LIPIDOSIS. In arteriolar nephrosclerosis and intercapillary glomerulosclerosis, both conditions in which protracted hypertension usually occurs, a high incidence of lipid deposition in renal arterioles was found (Table 4). In both acute and chronic glomerulonephritis and in nephrotic states the amount of arteriolar lipid found was essentially the same as in normal kidneys. Amyloidosis, lipid nephrosis, the renal lesion of multiple myeloma and unidentified types of tubular injury are included in the nephrotic group.

Perhaps the only unexpected finding in these groups is the failure of kidneys with chronic glomerulonephritis to reveal an increase of arteriolar lipid since prolonged hypertension is a common concomitant of this condition. In only 7 of the 15 cases of chronic glomerulonephritis was evidence of hypertension elicited before death, although in 5 others the heart was hypertrophied. In these 7 cases the mean incidence of arteriolar lipidosis was only 38.2%; this is well below the mean of other hypertensive groups. The low incidence of arteriolar lipidosis cannot be explained by the fact that many of those with chronic glomerulonephritis were quite young. The mean incidence of arteriolar lipidosis in 8 persons with this condition over the age of 40 was 29.2%. Nevertheless, there is substantial

TABLE 4. THE RELATION OF RENAL DISEASE TO RENAL ARTERIOLAR LIPIDOSIS

Disease	Number of Cases	Per Cent Arterioles With Lipid Mean	Average Amount of Lipid per Arteriole			
			Marked	Moderate	Slight	None
Intercapillary Glomerulosclerosis	20	70.4	1	11	8	0
Arteriolar Nephrosclerosis	34	69.8	9	20	5	0
Chronic Glomerulonephritis	15	30.6	0	3	11	1
Acute Glomerulonephritis	5	21.9	0	1	4	0
Nephrosis (Miscellaneous Types)	17	29.5	1	2	13	1
None	49	32.3	1	8	35	5
TOTAL	140	44.9	12	45	76	7

The 9 kidneys from persons with hypertension but without cardiac hypertrophy and the 30 kidneys from persons with only cardiac hypertrophy had more arteriolar lipid than did the kidneys from persons with neither of these findings. There was less arteriolar lipid in these 2 groups than in the group in which both hypertension and cardiac hypertrophy were co-existent. It is likely that the cases of hypertension without cardiac enlargement were chiefly ones in which elevation of blood pressure was of brief duration or of mild degree. Furthermore, it is probable that in many cases of cardiac hypertrophy in which no evidence of hypertension was obtained, the cardiac enlargement was due to other causes.

evidence that hypertension alone without apparent injury to renal tissue is associated with the deposition of fat in renal arterioles. In 19 persons with normal kidneys but with either a history of hypertension or with cardiac hypertrophy, the incidence of fat laden arterioles was 47.5% but in 30 persons with normal kidneys and neither hypertension nor cardiac hypertrophy the incidence was much lower, being 22.8%.

THE RELATION OF DIABETES TO RENAL ARTERIOLAR LIPIDOSIS. The incidence of renal arteriolar lipidosis is increased in diabetes (Table 5). The difference between diabetic and non-diabetic persons is not as striking as that between hypertensives and non-hypertensives. Nevertheless, the difference is statistically significant between the total groups of diabetics and non-diabetics and also between the diabetics and non-diabetics without hypertension or cardiac hypertrophy. The difference between the means of the diabetic and non-diabetic groups with both hypertension and cardiac hypertrophy is only 1.6 times the standard error of this difference and is therefore not statistically valid. It is probable that there is a greater tendency for hypertension than for diabetes to increase the incidence of renal arteriolar lipidosis and that this has diminished the difference between these latter groups. Although insufficient blood lipid determinations were available to establish the degree of hyperlipemia associated with the diabetes, the increased deposition of fat in arterioles of diabetics is most plausibly attributed to elevation of blood lipid.

TABLE 5. THE RELATION OF DIABETES TO RENAL ARTERIOLAR LIPIDOSIS

Group	Cardiac Hypertrophy	Number of Case	Per Cent Arterioles With Lipid Mean	Average Amount of Lipid per Arteriole			
				Marked	Moderate	Slight	None
Diabetic with Hypertension	Yes	24	67.5 ±3.9	5	10	9	0
Non-diabetic with Hypertension	Yes	25	57.9 ±4.8	4	11	10	0
Diabetic with Hypertension	No	6	61.8	0	4	2	0
Non-diabetic with Hypertension	No	3	22.4	0	0	3	0
Diabetic without Hypertension	Yes	12	51.2	2	4	6	0
Non-diabetic without Hypertension	Yes	18	35.7	0	6	10	2
Diabetic without Hypertension	No	16	41.2 ±5.7	0	5	11	0
Non-diabetic without Hypertension	No	36	23.9 ±3.4	1	5	25	5
All Diabetics		58	56.3 ±3.2	7 (12.0%)	23 (39.7%)	28 (48.3%)	0
All Non-diabetics		82	36.9 ±3.1	5 (6.1%)	22 (26.8%)	48 (58.6%)	7 (8.5%)

ARTERIOLAR LIPIDOSIS IN ORGANS OTHER THAN THE KIDNEY. The incidence of arteriolar lipidosis is increased in the spleen, pancreas and adrenal in hypertension (Table 6). In all of these organs, hyaline thickening of the arterioles is common in hypertension. In the heart, however, where hyalinization of arterioles is uncommon, little increase of lipid deposition was noted in hypertension. In the groups of mis-

TABLE 6. MEAN INCIDENCE OF ARTERIOLAR LIPIDOSIS IN ORGANS OTHER THAN THE KIDNEY

Group	Number	Spleen	Pancreas	Adrenal	Heart	Miscellaneous Organs	
Hypertensive	10	58.1%	63.7%	41.1%	9.4%	16	25.1%
Non-Hypertensive	10	34.2%	22.8%	7.0%	11.4%	8	12.3%

cellaneous organs, close correlation was noted between the observed incidence of arteriolar lipidosis and known incidence of hyaline arteriolar sclerosis. In such organs as the prostate, uterus, ovary and bladder, in which hyalinized arterioles are sometimes found in hypertension, a relatively high incidence of lipid deposits was also noted. In the testis, brain, diaphragm and thyroid, lipid deposits were seldom found in the arterioles of either the hypertensive or non-hypertensive groups.

The highest incidence of arteriolar lipidosis in non-hypertensive persons was found in the spleen (34.2%). While the incidence is not much greater than that observed in kidneys from non-hypertensive persons (29.8%), there was a marked difference in the degree of lipid deposition in the arterioles of these 2 organs. Of the 52 kidneys from non-hypertensives only 12 (23.1%) had more than slight deposits of fat in the arterioles, whereas of the 10 spleens from non-hypertensives, 6 had moderate or marked deposits of fat in the follicular arterioles. It is of interest that a relatively high incidence of lipid deposition is observed in the arterioles of the one organ, the spleen, that regularly undergoes arteriolar sclerotic changes in the absence of hypertension.

Discussion. The foregoing analysis discloses that the factors that influence the deposition of lipid in the intima of arteries and the walls of arterioles are much the same. Some lipid, even though it be minute in quantity, may be found in the arteries in the majority

FIG. 6. Lipid deposits in 2 groups of sclerotic tortuous arterioles and several single follicular arterioles of the spleen. Frozen section, Sudan IV stain (x 24).

of necropsies done at Bellevue Hospital, regardless of the age of the subject. The occurrence of renal arteriolar lipidosis is also very common. Advanced arterial and arteriolar lipidosis are both uncommon in the very young. The incidence of lipid deposition in both arteries and arterioles is increased in the presence of hypertension or diabetes. In non-hypertensive persons

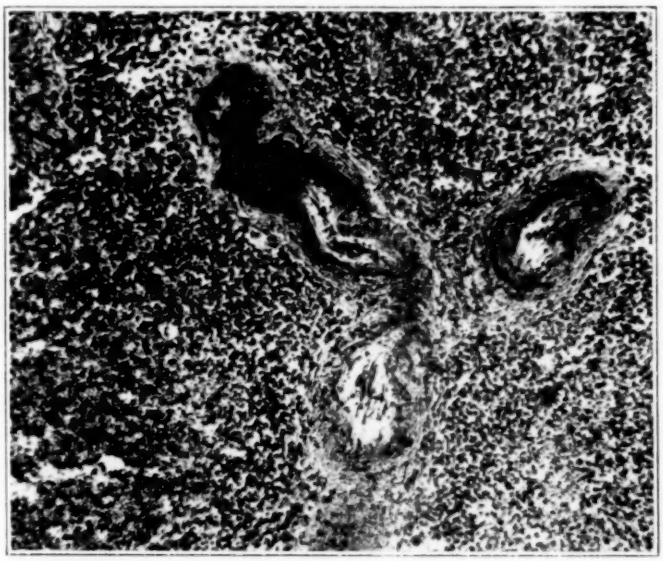


FIG. 7. Lipid deposits in the wall of a follicular arteriole of the spleen in a non-hypertensive person. Frozen section, Sudan IV stain (x 153).

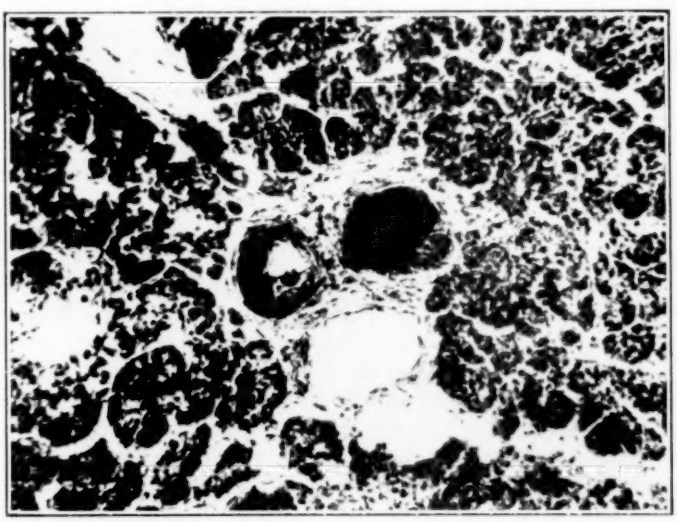


FIG. 8. Lipid deposits in hyalinized pancreatic arterioles of a hypertensive person. Frozen section, Sudan IV stain (x 183).

there is a gradual increase of the incidence of arteriolar lipidosis with advancing age. While there are few points of similarity in the manner in which fat is deposited in arteries and arterioles, there is one feature that is the same: namely, in both, fat tends to accumulate at branch orifices.

The differences between arterial and arteriolar lipidosis are largely superficial or secondary in character. None is irreconcilable with the thesis that lipid deposition at both sites results from a disturbance in the same underlying mechanism. Arteriolar lipidosis is more restricted in distribution than is arterial lipidosis. Unlike the latter, the arteriolar deposits are more abundant in women than in men. They are probably more directly influenced by hypertension and less so by hyperlipemia and advancing age than are arterial lipid deposits.

The differences in the character of the lipid and its intramural disposition offer more formidable objections to considering the deposits at both sites as part of the same process. The lipid found in the arterial intima is generally believed to be derived from blood plasma. There is no reason for regarding arteriolar lipid as having a different origin, especially since both types of deposits are influenced by much the same conditions. Differences in the appearance of the lipid at both sites may be attributed to a large extent to differences in thickness of the vessel walls and in thickness of the elastica. The following speculations are presented as an example as to how the intrinsic structure of the vessel might be of importance in determining the character of lipid deposited within them from the plasma. It is possible that the heavier internal elastic membrane of large arteries offers a more impenetrable barrier to the passage of fluid filtering through the endothelium than does the thinner elastic membrane of arterioles. Separation of doubly refractive cholesterol ester and the subsequent formation of free cholesterol crystals probably depends upon the deposition of free lipid masses and the action of phagocytic mononuclear cells. In the arterioles the lipid appears to impregnate the medial wall and is seldom separated into free aggregates. This may account for the failure of cholesterol to be partitioned from the total lipid mass. It is noteworthy that in old atheromatous plaques a large part of the lipid is often mixed with other materials and may not be doubly refractive.

The amount of lipid found in renal arterioles increases in proportion to the degree of hyaline sclerosis that is observed in them. Lipid deposition sometimes occurs before hyaline sclerosis has developed. Lipid deposition is commonly found in the arterioles of those organs whose arterioles frequently undergo hyalinization in the presence of hypertension. Conversely, it is seldom found in the arterioles of organs whose arterioles do not ordinarily become hyalinized even in severe protracted hypertension. Lipid deposition is regularly found in the splenic arterioles of rabbits fed with high cholesterol diets[3]. These observations suggest that lipid deposition plays an early and fundamental role in the development of the hyaline type of arteriolar sclerosis. It may further be conjectured that its role is essentially the same as in the development of atheromatous plaques of arteries. The occurrence of small streaks of lipid in the unhyalinized thin arterioles of non-hypertensive persons may be compared to the simple intimal streaks of arterial lipid that frequently antedate the formation of atherosclerotic lesions.

From previous analyses[1], it has been suggested that the role of blood pressure in the development of atherosclerosis is to provide a positive filtration

pressure against a permeable endothelial surface, thus enabling lipid-containing substances to enter the intima. It was further suggested in these analyses, from a study of the distribution of atherosclerotic lesions in the vascular system as a whole, that there is probably a threshold value of filtration pressure below which fluid entering the intima is largely devoid of lipid. Below this critical value the fluid that filters through the vessel walls is probably more like that which ordinarily traverses capillary membranes. If these principles are applied to arterioles then it may be suggested that elevation of renal arteriolar pressure in hypertension greatly facilitates the passage and accumulation of lipid in the arteriolar walls and leads eventually to hyaline thickening. Since lipid is occasionally found in the arterioles of some organs in non-hypertensive persons, it may be supposed that the normal range of arteriolar blood pressure in these situations exceeds the threshold for the filtration of lipid substances through the endothelium, but not to a degree sufficient to cause marked fat deposition. In hyperlipemia, lipid deposition should also be increased, since the fluid entering the arteriolar wall would have a higher content of this material.

In chronic glomerulonephritis the glomeruli and other units of renal parenchyma are largely destroyed before the onset of secondary hypertension. It is possible that the renal arteriolar pressure in this condition is consequently never greatly augmented, even though the arteriolar pressure is elevated throughout the rest of the body. This might account for the failure to find as great an increase of renal arteriolar lipidosis in renal hypertension as in other types.

For this explanation to be valid, it is necessary to assume that there are normally variations in blood pressure in the arteriolar beds of various organs. In those organs in which arteriolar lipidosis and hyaline arteriolar sclerosis are rare, the normal arteriolar blood pressure range should be lower than the hypothetical threshold value for the penetration of lipid containing fluid from the blood. Unfortunately accurate measurements of arteriolar pressures in various organs are not available. It would seem reasonable to assume that in organs in which there is a gradual diminution in vessel size and division by bifurcation occurs, much of the arterial pressure head must be dissipated before the systolic impulse is transmitted into very small arterioles, the size of afferent glomerular arterioles. On the other hand, in organs such as the kidney where many small arterioles arise directly from arteries several times their size, a higher level of arteriolar pressure may be maintained.

There are probably other factors besides intra-arteriolar blood pressure that determine the effective filtration pressure within arterioles. The extra-arteriolar tissue pressure must be a factor. It is noteworthy that in almost all sites except the kidneys in which arterioles commonly undergo hyalinization in hypertension, the arterioles are situated in loosely woven interstitial tissue and that the organs are not enclosed by unyielding capsules. This is true, for example, of the intestine, mesentery, periadrenal tissue, spleen and probably the pancreas. Where interstitial fluid pressure remains low in spite of increased arteriolar pressure, a greater positive filtration pressure is to be expected than if tissue fluid pressure rises concomitantly with arteriolar pressure.

In the spleen where rapid changes in volume occur due to the expulsion of large amounts of blood from the pulp intermittently, it is probable that there are greater variations in pulp pressure than in any other organ. There

must be periods of unusually low pulp pressure. This could account for the unusually high incidence of lipid deposition and arteriolar sclerosis in this organ, even in the absence of hypertension.

Summary and Conclusions. Lipid deposition in the walls of renal arterioles occurs as commonly as it does in the intima of large arteries. It is relatively infrequent and slight in the very young and increases in incidence slowly but progressively with advancing age in non-hypertensive persons. It is somewhat more common in hypertensive or diabetic women than in similar groups of men. There is no difference in sex incidence of renal arteriolar lipidosis in non-hypertensive persons or in whites and negroes.

The incidence of renal arteriolar lipidosis is significantly increased in all forms of hypertension except that associated with chronic glomerulonephritis. It is significantly increased in diabetes. It is not increased in renal diseases that are not associated with hypertension.

The incidence and severity of renal arteriolar lipidosis is increased in the presence of arteriolar sclerosis, although scanty lipid deposits are frequently found in arterioles that are otherwise unaltered. Evidence is presented that indicates that lipid deposition may be an early and essential feature in the hyalinization and thickening of arterioles observed in protracted hypertension. It is further suggested that elevation of arteriolar blood pressure or increase of the plasma content of lipid are important factors in the deposition of fat within arteriolar walls.

REFERENCES

1. **Anitschkow, N.:** Beitrc. z. Path. Anat. u. z. Allg. Path., **57**, 201, 1914.
2. **Fuller, R. H.:** Arch. Path., **32**, 556, 1941.
3. **Wilens, S. L.:** Arch. Int. Med., **82**, 431, 1948.

LIPOTROPIC EFFECT OF LIVER EXTRACT AND OTHER SUPPLEMENTS IN DIETARY INDUCED LIVER INJURY IN RATS*

By Victor A. Drill, Ph.D., M.D.
PROFESSOR OF PHARMACOLOGY
WAYNE UNIVERSITY COLLEGE OF MEDICINE
DETROIT, MICHIGAN

AND

Charles A. Hall, M.D.
POST-WAR FELLOW, ROCKEFELLER FOUNDATION, 1947-1948
NEW HAVEN, CONNECTICUT

(From the Department of Pharmacology, Yale University School of Medicine)

Attempts to treat liver damage in man have been based chiefly on experimental observations in which various substances have been studied for their effect in preventing liver injury induced by dietary means. Most of the emphasis of such work has been on the lipotropic action of choline and methionine and little or no attention has been paid to the possible effectiveness of substances such as yeast, hog stomach or liver extract.

The present study concerns the effects, in rats, of 5 dietary supplements in preventing hepatic lesions induced by 2 types of diets: a high-fat diet, and a low-protein diet. The supplements studied were choline, methionine, yeast, hog stomach (Ventriculin) and liver extract. The effects of these materials were controlled by daily measurements of food intake, to rule out effects of the supplements on appetite and protein intake, and supplements of casein were added to the basic diet further to control changes in protein intake. Choline was selected as a supplement because it is the most effective and best studied of the lipotropic agents[1,2,3,5,6,9,15], and to serve as a basis for comparison with the effects of the other supplements. Methionine was included because it has been found chiefly effective in preventing hepatic necrosis with a lesser degree of lipotropic activity[2,6,9,10,11]. Brewer's yeast has been studied but the results have been conflicting[6,10,15] and it was included for further evaluation and comparison with choline and methionine under controlled conditions.

Hog stomach (Ventriculin) was reported to be effective in treating children with pellagra that was accompanied by a fatty liver[4]. Serial liver biopsies in such children showed that Ventriculin had a marked lipotropic effect. As hog stomach had not been studied previously with experimental diets, it was included in the present study. Liver extract has recently been reported to have a marked lipotropic action in animals fed a high-fat diet[7]. It was included again particularly to observe any effects when low-protein diets were used to induce liver damage.

The effectiveness of these supplements in preventing the induced liver injury was determined by histological technique and by analyses for total liver lipids.

* This investigation was supported (in part) by a research grant from the Division of Research Grants and Fellowships of the National Institutes of Health, United States Public Health Service, and by a grant from Eli Lilly and Company.

Methods. The composition of each of the 3 diets used is listed in Table 1. Vitamins A and D were supplied by adding 5 drops of oleum percomorphum per kg. of diet to the melted lard as the diet was prepared. Each rat received a daily oral supply of the B vitamins as follows: thiamin, 20 μ gm.; riboflavin, 25 μ gm.; pyridoxine, 20 μ gm.; calcium pantothenate, 100 μ gm.

TABLE 1. COMPOSITION OF EXPERIMENTAL DIETS

	Diet I	Diet II	Diet III
Salt Mixture	3%	6%	4%
Casein	16%	6%	6%
Lard	51%	15%	15%
Cornstarch	30%	70%	72%
Sucrose	—	3%	3%
	100	100	100

Male rats of the Sprague-Dawley strain, weighing between 140 and 170 gm., were used. The number of animals per group is listed in the tables. Five animals of each diet and group were housed in individual cages, and their daily food intake was measured. Diet I was fed *ad libitum* for a period of 200 days. Liver biopsies were taken under ether anesthesia during this study from 5 animals in each group fed diet I, at the time intervals listed in Table 2. The same 5 animals were used for each biopsy. Diet II was also fed *ad libitum*. Of the groups fed Diet II, some animals were sacrificed at 150 days and the remainder after 200 days of the experiment (Table 3). When Diet III was fed, all animals were housed in individual cages and the food supplied was restricted to 8.0 gm. per day. Food intake measurements showed that practically all of this food was consumed each day. The animals receiving Diet III were sacrificed between the 60th and 75th day of the study.

Supplements Administered. Various groups fed the different diets received the following supplements*: (a) choline chloride, 40 mg. per day subcutaneously; (b) dl methionine, 40 mg. per day subcutaneously; (c) crude liver extract (Lilly, 1 U.S.P. unit per cc.) 1 cc. subcutaneously 3 times a week; (d) brewer's yeast, 0.25 gm. per rat per day, mixed with the diet; (e) hog stomach (Ventriculin), 0.5 gm. per rat per day, mixed with the diet.

With Diet I, a high-fat diet, the rats receive a large amount of calories as fat, and their total food intake and protein intake will decrease. Therefore, as a further control one group of rats was treated with the addition of 8% casein to the basic diet, the content of corn starch being decreased by 8%. The total amount of casein received by this group was therefore 24%. Similarly, with Diet II, a low-protein diet, one group received an additional 0.5% casein to control any small amount of protein added to the diet by the various supplements.

All liver sections, obtained at biopsy or necropsy, were stained with hematoxylin and eosin. In about half of the animals in each group frozen sections were made and stained with Sudan III. In a few cases Masson, reticulin, acid-fast stain and Best-carmine stain were also utilized. The remaining liver in 2 experiments was analyzed for total lipids by a modification of the method of Outhouse and Forbes[12].

Results. Diet I (High-fat Diet). Liver biopsies were obtained from 5 animals in each group at the time indicated in Table 2. At the first biopsy only the animals treated with liver extract or choline showed a normal hepatic histology. Supplements of methionine, casein or yeast offered only partial protection against the fatty change (Table 2) and the fatty change was greatest about the central vein. Ventriculin failed to prevent the infiltration of fat in the liver and the hepatic changes were as marked as those observed in rats fed only the basic diet. The changes produced by

* The authors wish to thank the Eli Lilly Company for supplying the Crude Liver Extract, the Parke, Davis Company for the Ventriculin; Meade Johnson and Company for the Oleum Percomorphum; Eli Lilly and Company and Wyeth Inc. for the methionine; the Fleischmann Laboratories for the yeast. The supplements contained: Brewers Yeast, Type 50-B, Fleischmann; Pyridoxine, 31 gamma/gm.; Pantothenic acid, 101 gamma/gm.; Inositol, 4.4 mgm/gm.; Choline, 3.6 mgm/gm.; Biotin, 2.2 gamma/gm.; Niacin, 493 gamma/gm.; Riboflavin, 73 gamma/gm.; and Folic acid, 24.5 gamma/gm. Ventriculin, Methionine, 1.64%; Riboflavin, 6.9 gamma/gm.; Choline, 3.92 mg./gm.; and Folic acid, 0.2 gamma/gm. Crude Liver Extract, Thiamin, 2.0-4.5 gamma/cc.; Nicotinic Acid, 100-140 gamma/cc.; Folic acid, 2.0-3.8 gamma/cc.; Methionine, 3 gamma/cc.; Riboflavin, 45.0-60 gamma/cc.; and Choline, 1.0-1.6 mg./cc. Total nitrogen; 9.3%, of which 53% is amino nitrogen.

TABLE 2. EFFECT OF SUPPLEMENTS ON HEPATIC TISSUE AT BIOPSY AND AUTOPSY OF RATS FED DIET I. SERIAL BIOPSIES WERE TAKEN ON 5 ANIMALS IN EACH GROUP AT THE TIME INDICATED. DATA INDICATE NUMBERS OF ANIMALS WITH PATHOLOGICAL CHANGES

Group	Liver Biopsy 85 to 90 days			Liver Biopsy 155 to 165 days			Autopsy 190 to 200 days		
	1 to 2+ Fat	3 to 4+ Fat	Fibrosis	1 to 2+ Fat	3 to 4+ Fat	Fibrosis	1 to 2+ Fat	3 to 4+ Fat	Fibrosis
Basic diet	0	5	1	0	5	4	0	5	4
Ventriculin	1	4	0	0	5	2	1	4	2
Methionine	3	0	0	2	1	1	2	2	1
Casein	3	1	0	3	1	0	4	0	0
Yeast	2	1	0	2	0	0	3	0	0
Liver Extract	0	0	0	0	0	0	0	0	0
Choline	0	0	0	0	0	0	0	0	0

Grading: 1 to 2+ = Less than half of each lobule with fatty change.
3 to 4+ = More than half of each lobule with fatty change.

TABLE 3. MICROSCOPIC LESIONS OF LIVER AT AUTOPSY OF ANIMALS RECEIVING SUPPLEMENTS TO THE BASIC DIETS

Figures indicate number of animals.

Group	Total Animals	1 to 2+ Fat	3 to 4+ Fat	Fibrosis	Average Total Liver Lipids in % (wet wt.) and S. E.
		Diet I (16% Protein, 51% Fat)			
Basic Diet	13	0	13	11	20.50% ± 1.72
Ventriculin	10	2	8	5	21.76% ± 1.38
Methionine	10	6	4	2	17.80% ± 2.46
Casein, 24%	9	8	0	0	15.46% ± 1.11
Yeast	10	5	1	0	11.22% ± 0.92
Liver Extract	10	0	0	0	8.84% ± 0.65
Choline	10	0	0	0	7.36% ± 0.64
		Diet II (6% Protein, 6% Fat)—150 Days			
Basic Diet	6	0	6	3	
Casein	7	1	6	3	
Ventriculin	6	0	6	3	
Methionine	6	2	3	0	
Yeast	6	1	0	0	
Liver Extract	6	0	0	0	
Choline	5	0	0	0	
		Diet II—200 Days			
Basic Diet	4	0	4	3	23.14% ± 2.94
Ventriculin	4	0	4	4	21.40% ± 7.26
Methionine	4	1	2	0	17.89% ± 8.20
Yeast	4	0	0	0	7.89% ± 0.86
Liver Extract	4	0	0	0	7.24% ± 0.56
Choline	3	0	0	0	7.21% ± 1.08
		Diet III (4% Protein, 6% Fat, Restricted Intake)—60 to 75 Days			
Basic Diet	10	0	8	0	
Methionine	10	6	0	0	
Yeast	10	1	0	0	
Choline	8	1	0	0	
Liver Extract	10	0	0	0	

Grading: 1 to 2+ = Less than half of each lobule infiltrated.
3 to 4+ = More than half of each lobule infiltrated.

the basic diet have been previously described[8,10]. At the second liver biopsy similar fatty changes were observed in the different groups, and fibrosis had developed in some of the animals that had previously shown a marked fatty change in the liver.

All of the animals fed the various supplements were autopsied between the 190th and 200th day of the study. Either supplements of choline or liver extract completely prevented fatty changes and fibrosis in the liver (Table 3). Methionine, casein and yeast gave only partial protection and supplements of Ventriculin were without effect (Fig. 1). The animals with marked fatty changes in the liver also developed fibrosis. Necrosis was not observed grossly or microscopically in any of the groups. The evaluation of the fatty change histologically correlated quite with total liver lipids (Table 3).

As judged by the gain in weight, the animals may be divided into 2 groups. Treatment with supplements of casein, choline or methionine produced the greatest increase in body weight (Fig. 2), but only the choline protected against hepatic injury. The animals receiving liver extract, yeast or Ventriculin gained the same amount of weight, but less than the rats treated with the other supplements. In this group only the liver extract offered good protection against liver injury. The gain in weight that the various supplements produced is not related to their lipotropic activity.

DIET II (LOW-PROTEIN DIET). The animals fed the various supplements were sacrificed in 2 groups, at 150 and 200 days of the study (Table 3). The findings were essentially the same at either time and will be discussed together. The main change histologically in the group fed only the basic diet was again the presence of large fat droplets which almost filled the cells, as previously described[8]. Fibrosis only developed in animals that showed a marked fatty change.

The same supplements that protected against hepatic changes with Diet I prevented the histological changes produced by Diet II (Table 3). If one compares the effect of each supplement with either diet the similarity is striking, with the exception of the yeast which was more effective

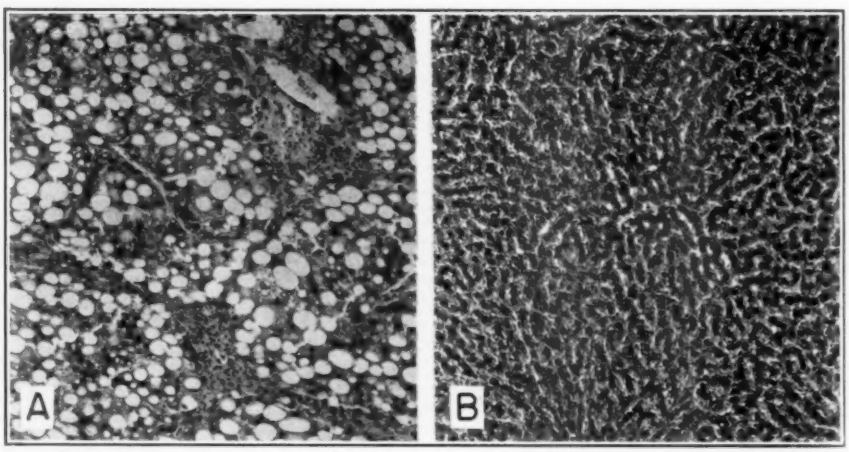


FIG. 1. Photomicrograph of liver section (x 150). (A) Untreated rat fed the high-fat (Diet I). (B) Effect of liver extract on liver tissue of a rat fed a high-fat diet (Diet I).

with Diet II, offering nearly complete protection. The results of the analyses for total liver lipids support the pathological findings. Necrosis was not observed, either grossly or histologically.

With the exception of methionine the various supplements produced a similar gain in weight (Fig. 2). Methionine produced the greatest increase in weight, but only poorly protected against hepatic injury. The lipotropic effect of supplements in the presence of low-protein diet was not related to the gain in weight produced.

Diet III (Low-protein Diet and Restricted Food Intake). The restriction of food intake to 8.0 gm. a day still produced fatty changes in the liver. However, the diet was fed for a shorter period of time and this effect occurred in only 8 of the 10 animals fed the basic diet. Histologically large fat droplets were present, as previously described with Diets I and II. Supplements of methionine again gave poor protection against the fatty changes and choline; yeast and liver extract gave the best protection. The diets were not fed sufficiently long to allow fibrosis to develop. Necrosis was not observed, grossly or microscopically.

The restriction of food intake to all animals receiving Diet III produced an initial decrease in weight in all groups (Fig. 3). All of the supplements then produced some increase in weight, but this change was again not related to the lipotropic effect of the substances.

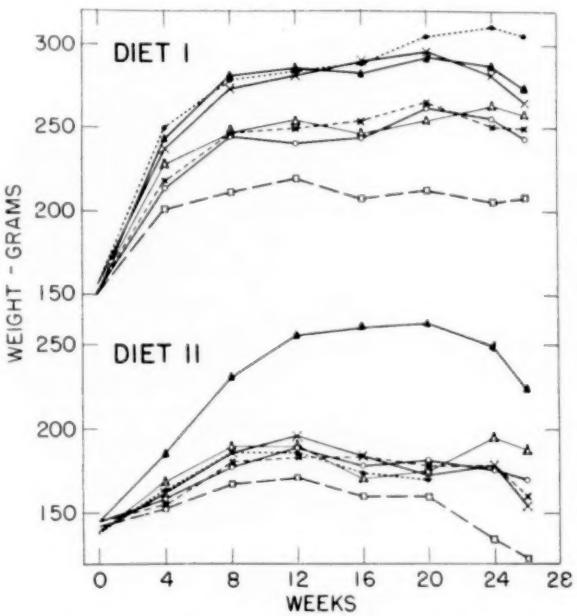


Fig. 2. Effect of supplements on change in weight of rats fed Diet I and Diet II. Legend for these graphs is the same as that for Fig. 3.

Discussion. Untreated rats fed the high-fat and low-protein diets developed similar lesions in the liver consisting of marked fatty change followed, depending on the length of time the diets were fed, by fibrosis. Such basic diets, in our hands, have not produced necrosis[8]. The choline was very effective in preventing the

fatty change and also the fibrosis that followed marked fatty infiltration. It was equally effective with the high-fat and low-protein diets. This lipotropic effect of choline is well known, and the findings here are similar to those of many previous investigators of dietary liver injury[1,2,3,5,6,9,15]. The effectiveness of the choline in preventing these lesions served as a basic line to compare the lipotropic effects of the other supplements.

Hall and Drill[7] recently reported that crude liver extract was effective in preventing the hepatic lesions produced by a high-fat diet. This supplement has now been found equally effective in preventing the hepatic lesions induced by the low-protein diets. Of all the supplements studied, liver extract was the most effective in preventing the induced hepatic injury.

The yeast supplements offered only partial protection when added to the high-fat diet and hepatic fibrosis did not develop. Better protection against hepatic damage was obtained with yeast with the low-protein diets. With both of the low-protein diets only 2 of 20 rats showed minor fatty changes in the liver. György and Goldblatt[6] found that a similar amount of yeast prevented both the necrosis and cirrhosis produced by a high-fat, low-protein diet. In the present study, one group of rats fed the low-protein diet received an additional 0.5% casein, both to control any increase in protein intake resulting from increased appetite and to control protein supplied by the yeast. This addition of casein as a control was without effect on the incidence of the hepatic lesions. Webster[15] obtained similar results by adding 2 gm. of yeast per day to the diet. Himsworth and Glynn[10] found yeast to have a marked lipotropic effect when substituted in a diet producing fatty change. The smallest amount that they used was about twice that of the present study.

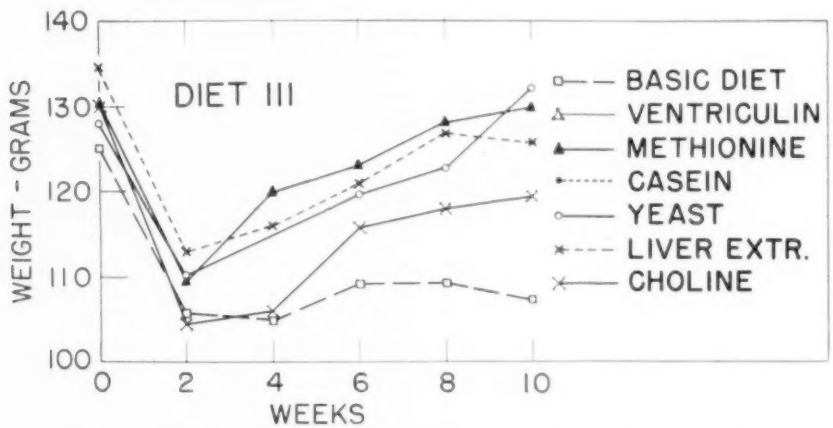


FIG. 3. Effect of supplements on change in weight of rats fed Diet III.

The methionine-treated animals showed the greatest variation in final lesions of all of the groups. Some animals had no fatty change, others only moderate infiltration, while some had the marked fatty change and fibrosis seen in the untreated animals. The effects of methionine in previous studies of dietary liver injury have been conflicting. It has been found

effective in preventing: the massive hepatic necrosis of Himsworth and Glynn[10,11]; the necrosis and cirrhosis of György and Goldblatt[6]; the cirrhosis of Daft *et al.*[7]; the hepatic necrosis of Green and Brunschwig[5]; the fatty change, fibrosis and necrosis of Handler and Dubin[9]; and the cirrhosis, and necrosis of Daft *et al.*[2]. In other reports, methionine was not effective in preventing fatty changes[5], and Rose *et al.*[13] found that when amino acids were used in place of dietary protein it had no lipotropic activity at all. It is very difficult to compare the different studies because of the great variation in diets, amounts of methionine, and the various techniques. Methionine is also difficult to evaluate because of its numerous metabolic uses. Treadwell *et al.*[14] concluded that under the circumstances of their study the intake of other amino acids determines how much is used as a lipotrope. In the present study the lipotropic effect of methionine was less than that of choline, yeast, or liver extract.

The Ventriculin was without effect on either the fatty changes or the fibrosis produced in the liver of rats. It is impossible to compare the findings here with the beneficial effects of Ventriculin obtained by Gillman and Gillman[4] in children with infantile pellagra. Although the circumstances were totally different, Ventriculin was studied with the above experimental diets as previous studies with this supplement are lacking. Although Ventriculin has no effect on the fatty change and fibrosis of the type produced here, it does not exclude the possibility that Ventriculin may be effective in preventing fatty livers of other types.

Calorie and Protein Intake. The data for food and protein intake of each group are set forth in Table 4. The effectiveness of lipotropic substances in preventing hepatic damage was not due to stimulation of appetite and a consequent increase in protein intake. With the high-fat diet (Diet I) several supplements did increase food intake. This is particularly true of

TABLE 4. AVERAGE DAILY FOOD, CALORIE, AND PROTEIN INTAKES OF ANIMALS FED BASIC AND SUPPLEMENTED DIETS

Group	Food gm. per Rat	Calories per Rat	Calories per 100 gm. per Rat	Protein gm. per Rat	Protein gm. per 100 gm. per Rat
		Diet I (16% Protein, 51% Fat)			
Basic Diet only	7.2	46.3	22.4	1.15	.555
Ventriculin	8.6	55.0	22.9	1.37	.569
Methionine	9.1	58.4	21.8	1.45	.544
Casein, 24%	8.8	56.7	20.8	2.12	.788
Yeast	8.1	52.1	22.0	1.30	.548
Liver Extract	8.0	51.6	21.6	1.28	.537
Choline	9.1	58.5	22.1	1.45	.550
		Diet II (6% Protein, 6% Fat)			
Basic Diet only	10.2	42.8	27.2	.614	.391
Casein, 6.5%	11.6	48.3	28.6	.748	.443
Ventriculin	11.3	47.1	27.7	.677	.398
Methionine	16.0	67.1	30.7	.962	.445
Yeast	12.5	52.1	31.3	.748	.447
Liver Extract	12.3	51.5	30.6	.739	.438
Choline	11.3	47.3	27.7	.680	.398
		Diet III (4% Protein, 6% Fat, Restricted Intake)			
Basic Diet only	7.6	31.8	29.6	.304	.283
Methionine	7.9	33.0	27.2	.315	.260
Yeast	7.6	31.9	26.8	.305	.257
Choline	7.6	31.8	28.3	.305	.268
Liver Extract	7.9	33.0	27.3	.315	.261

methionine and choline, but only the choline effectively prevented the hepatic lesions. Liver extract produced the least effect on food intake, and yet had a marked lipotropic effect. Thus the data show absolutely no correlation between protein intake and lipotropic effect. The greatest increase in protein intake was produced by the addition of 8% casein (24% casein group). This large addition of casein did not prevent fatty changes in liver, but only reduced the severity of the lesion (Tables 3 and 4).

With Diet II, one group received an additional 0.5% casein (6.5% casein group) to serve as a control for possible increases in food intake produced in the other groups. With both Diets II and III (Table 4) there was no correlation between calorie and protein intake and lipotropic effects of the supplements.

There is also no correlation between the gain in weight of the various groups and the lipotropic activity of the various supplements (Figs. 2, 3).

Choline Content and Lipotropic Activity. The daily intake of choline provided by the various supplements is listed in Table 5. The definite lipotropic activity of the yeast with the low-protein diets is not due to the choline content of the yeast. The Ventriculin treated animals received twice as much choline as the yeast-treated animals, but had markedly fatty livers. The effect of the yeast was much greater than that obtained by Himsworth and Glynn[10] with 4 mg. of choline per rat per day. The ineffectiveness of the methionine supplements also shows that the lipotropic effect of the yeast is not due to its small methionine content.

Liver extract had the greatest lipotropic effect and the least content of choline of all of the supplements (Table 5). Again, this amount of choline is much less than 4 mg. of choline required to prevent fat accumulation in the liver[10]. Further, the 4 mg. of choline per day only prevented fatty livers for about 34 days and abnormal amounts of fat were present at 66 days, despite continued choline administration. In the present studies the diets were fed for a much longer period of time. Daft, Sebrell and Lillie found 20 mg. of choline per day to be the lowest effective dose protecting against lesions produced by a 4% protein-5% fat diet.

TABLE 5. CHOLINE INTAKE OF SUPPLEMENTED GROUPS

Supplement	Choline Content	Diet I	Diet II	Diet III
Choline		40.0	40.0	40.0
Ventriculin	3.92 mg./gm.	2.07	1.85	—
Yeast	3.6 mg./gm.	0.97	0.88	0.86
Liver Extract	1.0-1.6 mg./cc.	0.56	0.56	0.56

The lipotropic effect of the yeast and liver extract does not appear to be due to the choline content of these supplements. These supplements may contain an unknown choline precursor or an unknown lipotropic substance.

Summary. 1. Three basic diets, either high in fat or low in protein, produced fatty changes and fibrosis in the liver of rats.

2. Supplements of crude liver extract were as effective as choline in completely protecting against the hepatic damage produced by all 3 diets.

3. Brewer's yeast offered partial protection against liver damage induced by the high fat diet, and nearly complete protection of animals fed the low protein diets.

4. Supplements of methionine gav

poor protection against the liver injury produced by either of the 3 diets. Hog stomach was without lipotropic effects.

5. The lipotropic effects of liver extract and brewer's yeast is not due to a stimulation of appetite with a consequent increase in protein intake. Even a supplement of 8% casein to the basic diet was not as effective as liver extract.

6. Liver extract, and perhaps also yeast, may contain an unknown choline precursor or an unknown lipotropic substance.

REFERENCES

1. **Blumberg, H.**, and **McCollum, E. V.**: Science, **93**, 598, 1941.
2. **Daft, F. S., Sebrell, W. H.**, and **Lillie, R. D.**: Proc. Soc. Exp. Biol. and Med., **50**, 1, 1942.
3. **Daft, F. S., Sebrell, W. H.**, and **Lillie, R. D.**: Ibid., **48**, 228, 1941.
4. **Gillman, T.**, and **Gillman, J.**: Arch. Int. Med., **76**, 63, 1945.
5. **Green, J.**, and **Brunschwig, A.**: Proc. Soc. Exp. Biol. and Med., **61**, 348, 1946.
6. **György, P.**, and **Goldblatt, H.**: J. Exp. Med., **75**, 355, 1942.
7. **Hall, C. A.**, and **Drill, V. A.**: Proc. Soc. Exp. Biol and Med., **69**, 3, 1948.
8. **Hall, C. A.**, and **Drill, V. A.**: Ibid., **70**, 202, 1949.
9. **Handler, P.**, and **Dubin, I. N.**: J. Nutrition, **31**, 141, 1946.
10. **Himsworth, H. P.**, and **Glynn, L. E.**: Clinical Science, **5**, 93, 1944.
11. Idem: Ibid. **5**, 133, 1944.
12. **Outhouse, E. L.**, and **Forbes, J. C.**: J. Lab. and Clin. Med., **25**, 1157, 1939.
13. **Rose, C. S., Machella, T. E.**, and **György, P.**: Proc. Soc. Exp. Biol. and Med., **64**, 352, 1947.
14. **Treadwell, C. R., Tidwell, H. C.**, and **Gast, J. H.**: J. Biol. Chem., **156**, 237, 1944.
15. **Webster, G. T.**: J. Clin. Invest., **21**, 385, 1942.

EOSINOPHILIA IN INFECTIOUS MONONUCLEOSIS

By Robert E. Kauffman, M.D.
ASSISTANT IN MEDICINE
NEW YORK, NEW YORK

(From The Lenox Hill Hospital)

Although numerous authors have described individual cases of infectious mononucleosis showing an eosinophilia, there has been no systematic tabulation of cases with this finding. I have been impressed by the frequent occurrence of an eosinophilia in this disease, and have summarized the cases in which records of blood smears done by myself were available. Of 82 such patients, 34 (41.5%) had 4% or more eosinophils in at least one smear, frequently in the acute febrile stage; 22 individuals (26.8%) of the entire series showed 5% or more at some time. The maximum eosinophilia was 8% in 2 cases, 9% in 2, and 11% in 1. To compare this group of patients, most of whom were not hospitalized, with a group who were hospitalized, I reviewed the charts of all proved cases in one hospital during the past 10 years. Of 62 patients, 15 (24.2%) had 4% or more eosinophils in at least 1 smear, and of the entire series 8 (12.9%) had 5% or over at some time. The maximum eosinophilia was 8% in 1 case, 9% in 2 and 10% in 1.

I studied the clinical picture and the hematologic and serologic findings in all patients in both series, and include only those cases in which there seemed to be no doubt about the diagnosis. For proof it was considered necessary for one or more blood smears to show numerous "atypical mononuclear cells characteristic of infectious mononucleosis." In addition, either the clinical manifestations had to be compatible with the diagnosis or the heterophil antibody reaction positive in a titer considered pathognomonic of infectious mononucleosis[6].

There is a difference of opinion among authorities concerning the behavior of the eosinophils in this disease. Wechsler, Rosenblum, and Sills[15] state: "During the early stages of the disease, the eosinophiles were either absent or present in small numbers. During convalescence, they were frequently increased." Bernstein[2] wrote: "As in other infectious diseases, eosinophils are typically suppressed during the acute phases. On the other hand, during convalescence the eosinophils commonly rise to 5 or 6% as in several of our cases; infrequently to 9%, to 12%, or even 15%." According to Foord and Butt[4], "In the active stage of the disease, the eosinophils do not disappear entirely and not uncommonly during convalescence are slightly increased in number." Raeburn[13] made the following brief note: "The eosinophiles may be slightly increased." And in Glanzmann's monograph[5], he states: "The eosinophiles may, as with other infections, diminish or entirely disappear. After the fall of the fever they increase and not rarely one sees a real post-infectious eosinophilia (7-15%). There are also cases which show a definite eosinophilia even during the stage of fever." My own observations show that an eosinophilia of 4% or more during the acute stage of the disease is much more common than one would expect from these reports or from theoretical considerations.

There are two reasons why I have taken 4% as an abnormal eosinophil level and any lower percentage as normal. The first is that although the authors of several textbooks[12,14,16] give 4% as the upper limit of normal, others[7,11] state that 3% is the maximum normal. The second and more important reason is that infectious mononucleosis is an acute infection, and one would expect by analogy to most other acute infectious diseases to find a decreased eosinophil percentage rather than an increase or even the maximum normal. Lowell and Wellington[9] state that "A lowering of the eosinophil count was observed in the majority of patients with acute infectious states, whether of bacterial or virus origin."

In studying the individual cases of various authors, it was found that the percentage of patients with an eosinophilia is often greater than they themselves realized. For example, Bernstein[2] in his series of 65 cases had two with an eosinophilia of 4% and 6%, presumably during the acute stage. In addition he had "several with 5% or 6% during convalescence." It is difficult in this disease to determine when the acute stage ends and convalescence begins, since there may be little relationship between the fever, symptoms, physical examination, blood smears, and sheep cell agglutination reaction. Glanzmann[5] had 1 case with 10% eosinophils on the second day of illness and 15% on the sixth day; another with 7% on the second day and 5% on the tenth day; and "some cases with a postinfectious eosinophilia of 7-15%." Foord and Butt[4] listed 38 cases with blood smears, and examination of these shows that 4 patients had eosinophil counts of 4, 4, 6, and 7%. Thus 11% of their cases had 4% or more on at least one smear. Becker[1] had 6 cases with smears recorded and one had an eosinophilia of 9%. Kruger, Wallace, and Penchansky[8] mention the differential counts of only 3 of their 63 cases, and of these one had 8% eosinophils and one had 13 to 21% on several occasions. Of the 4 cases reported by deVries[3], 2 showed a maximum eosinophilia of 8½% and 6%. Marr[10] gives the blood counts of 22 cases, of which 4 (18%) had an eosinophilia: 4, 5, 5, and 8%. In the very large series of Wechsler, Rosenblum, and Sills[15] there were 74 patients out of 556 with infectious mononucleosis who showed 6% or more eosinophils. This is 13%; but they state that 17 of these patients had other conditions frequently accompanied by an eosinophilia, so after eliminating these cases, the number with an eosinophilia of 6% or over is 10% of the total. Undoubtedly the percentage with 4% or more would be considerably higher. Five of their cases had 15% or more eosinophils for which no other cause could be demonstrated.

It should be pointed out that very few of the patients with eosinophilia in either my private or hospitalized series were allergic or had any other known cause for an eosinophilia; and the eosinophil percentage usually returned to normal during or shortly after convalescence. This eliminates the possibility that only individuals who were allergic or had some other cause for an eosinophilia showed the increase. When a blood smear shows numerous atypical cells of the mononuclear series, especially but not necessarily with a low percentage of polymorphonuclear cells and a shift to the left, an eosinophilia of 4 to 10% or slightly higher should not cause confusion but should help to confirm the diagnosis of infectious mononucleosis. However, there are 2 other common diseases—infectious hepatitis and rubella—in which the blood smear may occasionally be almost indistinguishable from that in infectious mononucleosis. To add further difficulty to

the differential diagnosis, the liver disturbance in infectious mononucleosis is clinically identical with that in infectious hepatitis; and one variety of rash in infectious mononucleosis is the same as the one seen in rubella. In those instances one must rely on repeated sheep cell agglutination tests, on examination of the patient's close contacts, and on one's clinical judgment.

Conclusions. 1. An eosinophilia during the acute stage of infectious mononucleosis is not rare.

2. In a personal series of 82 cases, 41.5% had 4% or more eosinophils and 26.8% had 5% or more, frequently in the acute febrile phase.

3. In a hospital series of 62 cases, 24.2% showed 4% or over and 12.9% showed 5% or over.

4. In the differential counts recorded in the series of several authors there was an eosinophilia of 4% or more in 10 to 20% of cases.

5. A smear showing numerous atypical mononuclear cells, especially with a decrease in percentage of neutrophils and a shift to the left, suggests infectious mononucleosis; and an eosinophilia of 4 to 10% or slightly higher is another point in favor of that diagnosis.

REFERENCES

1. **Becker, H.**: München med. Wchnschr. **78**, 1594, 1931.
2. **Bernstein, A.**: Medicine, **19**, 85, 1940.
3. **deVries, S. I.**: Acta med. Scand., **95**, 552, 1938.
4. **Foord, A. G.**, and **Butt, E. M.**: Am. J. Clin. Path., **9**, 448, 1939.
5. **Glanzmann, E.**: Abhandl. a. d. Kinderheilk. u. ihr. Grenzgeb., **25**, 1, 1928-1930.
6. **Kaufman, R. E.**: Ann. Int. Med., **21**, 230, 1944.
7. **Kracke, R. R.**: Color Atlas of Hematology, Philadelphia, J. P. Lippincott, 1947.
8. **Kruger, A. L., Wallace, A. W.**, and **Penchansky, S. J.**: Ann. Int. Med., **23**, 945, 1945.
9. **Lowell, F. C.**, and **Wellington, M. S.**: Bull. New Eng. Med. Center, **7**, 269, 1945.
10. **Marr, W. L.**: Texas State J. Med., **32**, 603, 1937.
11. **Meakins, J. C.**: The Practice of Medicine, St. Louis, C. V. Mosby, 1946.
12. **Piney, A.**: Synopsis of Blood Diseases, London, Heinemann, 1942.
13. **Raeburn, C.**: J. Roy. Army Med. Corps, **87**, 78, 1946.
14. **Todd, J. C.**, and **Sanford, A. H.**: Clinical Diagnosis by Laboratory Methods, Philadelphia, W. B. Saunders, 1947.
15. **Wechsler, H. F., Rosenblum, A. H.**, and **Sills, C. T.**: Ann. Int. Med., **25**, 236, 1946.
16. **Whitby, L. E. H.**, and **Britton, C. J. C.**: Disorders of the Blood, London, J. & A. Churchill, 1942.

PROGRESS
OF
MEDICAL SCIENCE

OPHTHALMOLOGY

UNDER THE CHARGE OF

WILLIAM L. BENEDICT, M.D.
HEAD OF SECTION OF OPHTHALMOLOGY, MAYO CLINIC

AND

HENRY P. WAGENER, M.D.
ASSISTANT PROFESSOR OF OPHTHALMOLOGY, MAYO FOUNDATION
ROCHESTER, MINNESOTA

LOSS OF VISION AFTER DISTANT HEMORRHAGE

BY ROBERT W. HOLLENHORST, M.D.

AND

HENRY P. WAGENER, M.D.
SECTION ON OPHTHALMOLOGY, MAYO CLINIC
ROCHESTER, MINNESOTA

PHYSICIANS have known for centuries that unilateral or bilateral serious or even total loss of vision can occur suddenly and remain permanently after hemorrhage from a tissue or organ remote from the eyes. The loss of vision may be noted immediately after a single massive hemorrhage, but it seems more likely to occur after a series of hemorrhages which are not necessarily massive. Its onset may be delayed for several days after the cessation of bleeding or after the last episode of bleeding. The variation in types of visual defects present in individual cases suggests that the responsible lesions are located at times in the brain, at times in the optic nerves, and at times in the retina.

Loss of vision resulting from distant hemorrhage does not occur with great frequency, but it is nonetheless an important entity and has been the subject of a number of reports and compilations in the literature. Many of the authors have been interested especially in the mechanism of the injury to the visual system. Just before or immediately after fainting, either from loss of blood or from some other cause, many individuals complain of transient blurring of vision or even of complete blindness which clears up without residuals after a short period. It is assumed generally that this transient loss of vision is similar to that which is associated with postural hypotension and is caused by relative ischemia of the retina similar to the ischemia of the brain which produces the syncope. It is possible that the failure of the vision to return after hemorrhage in some cases is due simply to longer or more severe deprivation of blood supply necessary to the retina or some other part of the visual pathway. How-

ever, it is difficult to explain solely on this basis cases in which the onset of loss of vision is delayed for several days after the hemorrhage. And, since histologic studies have been possible in only a few instances, and experimental attempts to reproduce the syndrome have been few, the exact nature and location of the lesions responsible for the loss of vision and the mechanism of their production are still largely unsettled problems.

Apparently the first mention of this condition was made by Hippocrates[25]. He rather laconically stated: "After the vomiting of blackish sometimes bloody matter, the patient complains of headache and the eyes do not see." The first comprehensive paper on this subject is that of Sigmund Fries[14], who, in 1876, collected from the literature of the previous 235 years 106 cases which he discussed. He could find no note on this entity in the first complete work on ophthalmology, that of George Bartisch in 1583. He stated that the first clear-cut report was that of Nicholas Fontanus in 1641 in which the loss of vision followed the letting of blood. Pergens[33], in 1896, confined his search of the literature to those cases of amaurosis or amblyopia resulting from hematemesis, and he was able to find 62 such cases. Many of these had been previously reported by Fries. Pergens called particular attention to the writings of Trnka de Krzowitz ("Historia Amauroseos," 1781) who gave a summary of a large number of cases of amaurosis from different causes. Amaurosis from hematemesis was classed with that caused by hemorrhages, sanguinary emissions, childbirth, ordinary vomiting, diarrhea, cholera, prolonged lactation and other debilitating conditions.

Singer[43] in 1904 compiled the data on 198 cases, the first 106 of which were those reported by Fries. His is the most complete article in the literature. Since then many additional cases have been reported. In 1912, Zentmayer[57] collected 24 additional cases from the literature. In 1922, Terson[47] reviewed 250 publications, and in 1924, Harbridge[21], 240 cases. Fink[12], in 1924, compiled from the literature reports of 130 cases of acute transitory blindness which occurred post partum or was associated with severe menorrhagia or metrorrhagia. He stated the prognosis in these cases was usually good. In 1949, Locket[31] found 44 cases in the literature from 1924 until 1947, and to these he added 3 of his own. We were able to find 14 additional cases reported in the literature during this same period, the cases of Ballantyne[1], Clegg[1], Enriquez[10], Milew and Pierach[32], Pines[35], Scheffler[41], Walsh[52] and Wolff[56], and in this paper we wish to add 5 additional cases encountered at the Mayo Clinic. Thus considerably more than 300 cases have been reported in the literature to the present, and undoubtedly many others have not been reported.

Sex of Patients. Among the 174 patients whose cases were collected by Singer[43], 79 (45.4%) were males and 95 (54.6%) were females. Females are apparently more numerous because of a much greater incidence of hemorrhage among women as a consequence of menstruation, childbirth and abortion. Loss of vision from hematemesis, however, occurs predominantly in males. Singer stated that among 66 patients who had bleeding from the stomach or intestine with accompanying loss of vision, 50 (76%) were males and 16 (24%) females. The youngest patient in whom this syndrome was noted was a child 2 years of age; this case was reported by Gooch[17] in 1830. Loss of vision occurred shortly after the application of 6 leeches to the forehead for the treatment of hydrocephalus. The

oldest patient whose case has been reported was 77 years of age; amaurosis in this case followed bloodletting.

THE HEMORRHAGE. The site of the hemorrhage was given in 189 of 198 cases reported by Singer. Among these, the source of bleeding was the stomach or intestine in 76 (40.2%), the uterus (including menstrual disorders, childbirth, neoplasms, spontaneous and induced abortions and so forth) in 62 (32.8%), bloodletting (venesection, cupping, leeches) in 27 (14.3%), epistaxis in 14 (7.4%), wounds in 6 (3.2%), hemoptysis in 2 (1.05%), and urethral bleeding in 2 (1.05%). It is interesting that in the most recent compilation, that of Locket[31], the statistics are approximately the same, with the exception that the cases due to bloodletting have decreased in number so that there is just 1 case, that of a man, 23 years old, with multiple sclerosis who was reported by Duggan[7] to have lost his vision 2 weeks after giving 2 donations of blood of 500 cc. each within 48 hours. The possibility that this actually was a case of retrobulbar neuritis due to multiple sclerosis would have to be considered. Stirling[44] reported the only recorded case of amaurosis from loss of blood following extraction of a tooth. The patient, however, was a hemophiliac.

It has been frequently observed and commented on that traumatic hemorrhage, no matter how severe, rarely produces loss of vision of this character. The reason for this has never been adequately explained. Furthermore, loss of vision only rarely follows an initial hemorrhage, but usually comes after repeated episodes of bleeding. Consequently, it has been said that blindness due to loss of blood never occurs except in chronically ill individuals. By and large, this appears to be true. In spite of the thousands of severely wounded soldiers treated during recent wars, reports of blindness following traumatic hemorrhage have been few. Thus, Heine[23] stated that not a single case was noted in the Franco-Prussian War of 1870 to 1871. Pincus[34] reported 2 instances in World War I, both in healthy soldiers. Each became blind after amputation of a limb after he had lain on the battlefield bleeding for several days. According to Duke-Elder[9], a similar case was reported by Pröll[36] in 1907 and another by Terrien[46] in 1921. The vision of Cox's[6] patient was reduced to light perception after a severe crushing injury of the chest followed by hematemesis and unconsciousness. Peripheral vision recovered gradually, but absolute central scotomas persisted. Carlini's[3] patient suffered from blindness from severance of a radial artery while chopping wood.

So far it has not been possible to determine either the minimal quantity of the loss of blood or the minimal duration of bleeding following which loss of vision may occur. Patients' estimates of both of these factors are notoriously inaccurate. However, Hinton and Davis[24] do not regard a gastrointestinal hemorrhage as massive unless it is associated with signs of shock: that is, systolic blood pressure of less than 100 mm. of mercury, rapid pulse, perspiration, erythrocyte count of 2,500,000 or less and a value of hemoglobin of 50% or less. Apparently, it is not possible to estimate the amount of blood lost by the ophthalmoscopic appearance of the ocular fundi or defects in the visual field.

ONSET AND DEGREE OF OCULAR DEFECTS. The onset of the visual loss is usually instantaneous, but it may come on gradually over the course of several hours, and rarely it may progress for several days. Also, if the initial loss of vision has not been complete, a subsequent hemorrhage may cause further

blindness. In 120 cases, Singer[43] was able to determine the time of onset of blindness after the occurrence of the hemorrhage (Table 1).

TABLE 1.—TIME OF ONSET OF BLINDNESS WITH RELATION TO THE HEMORRHAGE (MODIFIED FROM SINGER[43])

Time of onset after hemorrhage	*Cases*	*%*
During the hemorrhage	10	8.3
Immediately after	14	11.6
The first 12 hours	17	14.2
12 to 48 hours	23	19.2
3 to 10 days	47	39.2
14 days	5	4.2
18 to 60 days	4	3.3

The loss of vision varies considerably in degree and type. It may be unilateral (12.4% of Singer's cases) or bilateral, and may range from complete blindness of both eyes or blindness in one eye and only slight loss in the other, to only very mild loss of vision in one eye. Accompanying the loss of vision there may be other symptoms, some of them probably on the basis of cerebral ischemia. Thus, there may be sensory and motor disturbances, aphasia, deafness, headache, eye-ache, cramps, amnesia, faintness, tinnitus, nystagmus, palpitation, thready pulse and sometimes coma. There may be signs suggestive of cerebral thrombosis.

The defects in the fields of vision when it is possible to plot them, vary greatly in type. There is usually marked depression of the visual fields with wide sector defects. Sometimes irregular vertical or horizontal hemianopsia is present. According to Traquair[50], these always include the fixation area. Pincus[34], Wolff[56] and Kümmell[29] stated that the most typical disturbance of the visual field is an inferior altitudinal anopsia in one or both eyes corresponding to loss of function of the upper half of the retina. Grout[20] noted loss of the lower field in 23%, concentric contraction in 20%, central scotomas in 13%, and homonymous hemianopsias in 10%. The changes may be much more marked in one visual field than in the other, but usually any defect present is absolute or almost so; this indicates very severe damage. Kümmell[29] thought it probable that homonymous defects resulted from emboli or thrombi in the vessels supplying the optic tracts or the optic radiations.

Usually the affected eyes have dilated and fixed pupils when seen shortly after onset. The ophthalmoscopically visible lesions vary almost as much as do the field defects. And, as in the case of the field defects, the type of lesion present depends to some extent on the time that has elapsed since the onset of the loss of vision. No statistics are available on the relative incidence of the various changes visible in the ocular fundi. Occasionally the fundi appear perfectly normal. Sometimes only attenuation of the retinal arterioles is seen. The most common picture seems to be that of an ischemic optic neuritis. The optic disks are pale and edematous, with elevation of several diopters. The retinal arterioles are considerably attenuated. The retinal venules are mildly distended and tortuous. A few hemorrhages and exudates may be present in the retina near the optic disks, and there is usually some edema of the retina principally in the macular areas. Sometimes the ophthalmoscopic appearance is that of closure of the central retinal artery or of one of its branches, with pallor and superficial edema of the involved portion of the retina, fragmentation of the blood stream in the arterioles and venules, perhaps a cherry-red spot at the fovea, and in the later stages pallor of the optic disk and narrowing of the arterioles.

In all cases in which changes could be seen ophthalmoscopically in the early stages, optic atrophy developed subsequently. Most patients who were

seen several months after the loss of blood occurred had well-developed optic atrophy and attenuated arterioles. Some cases in which normal ocular fundi or only slight pallor of the disks and slight attenuation of the arterioles were noted, have had persistent central scotomas, and have been thought to be instances of retrobulbar neuritis. In a case cited by Watkins, Wagener and Brown[53] papilledema of 4 to 5 diopters in the left eye and 1 diopter in the right eye developed after recurrent bleeding from a gastric ulcer. Since central vision and visual fields were normal, and since the spinal fluid was under 40 cm. of water pressure, the papilledema was thought to represent "choked disk" rather than optic neuritis. At necropsy no lesions were found in the brain or meninges. These authors thought that the papilledema was due probably to local reaction of the tissues of the optic nerves to anoxemia that resulted from loss of blood. Foerster's[13] case was similar.

Unfortunately, histopathologic studies have been carried out in only 6 cases of this type. The studies of Gooch[17] in 1830, whose patient came to necropsy 8 days after the onset of blindness, were incomplete, as were those of Hirschberg[26], whose examination was done 3½ years after the onset of blindness, and of Esquirol[11], whose patient died 10 years after his loss of vision occurred. However, Ziegler[58], in a patient who bled from the stomach and died 23 days after onset of her blindness, found fatty degeneration of the nerve fibers and ganglion cells in the retina as well as many fat-filled cells in the optic nerve near the lamina cribrosa. He ascribed these changes to ischemia due to local anemia and arterial constriction. Of importance are the pathologic findings of Goerlitz[15] and Seese[42], who examined their patients at necropsy 11 and 5 days respectively after the onset of blindness. They found that the essential change was that of degeneration of the ganglion cells of the retina, with, probably as a secondary manifestation, fatty degeneration of the retina and of the optic nerves. Rählmann[38] found marked endarteritis in the retinal vessels but probably these findings must be disregarded because the patient had severe parenchymatous nephritis. Holden[28], in exsanguination experiments on dogs, found the same degeneration of the third neuron of the retina (the ganglion cells) as did Goerlitz[15] and Seese[42]. According to Duke-Elder[9], Uhthoff found similar changes in his experimental studies. Holden also noted degenerative changes in the optic nerves, chiasm and tract (ascending atrophy?), but no changes in the ganglion cells of the lateral geniculate bodies, anterior quadrigeminal bodies or the cortical visual areas.

According to most authors, the vision lost is seldom regained completely in cases of this type. Permanent residual defects are the rule. Thus, Locket[31], in reviewing 29 cases, found complete recovery in 4 (14%), partial recovery in 14 (48%), in 5 of which the improvement was slight, and no recovery in 11 (38%). Singer[43] compiled a table showing that the prognosis for recovery varies notably with the lapse of time between the hemorrhage and the onset of blindness (Table 2).

The degree of recovery in different cases varies and to make an accurate prognosis in a given case appears to be difficult. Barr[2] stated that the prognosis is least favorable in cases in which the hemorrhage was from the stomach.

None of the 5 patients whose cases we wish to report were seen during the early phase of the visual loss. Consequently it is possible only to conjecture as to the ophthalmoscopic find-

TABLE 2.—RELATION OF TIME OF ONSET OF LOSS OF VISION TO TENDENCY TO RECOVERY (MODIFIED FROM SINGER[33])

Time of onset after hemorrhage	*Total cases*	*Improvement*			
		None to worse		*Some to complete recovery*	
		Cases	*Per cent*	*Cases*	*Per cent*
During hemorrhage	9	7	77.8	2	22.2
Immediately to 12 hours	31	9	29	22	71
12 hours to 10 days	65	38	58.5	27	41.5
Longer than 10 days	8	4	50	4	50

ings at the time of onset of the blindness.

Report of Cases. CASE 1. A woman, 48 years old, was seen 7 months after she had lost vision in the left eye. She had passed tarry stools on the 4 days preceding the onset of blindness in the left eye. It was discovered later that the source of the bleeding was a large leiomyoma of the lesser curvature of the stomach. Her referring physician stated that at the time of loss of vision the concentration of hemoglobin in the blood was 30%. He had found a small hemorrhage in the left retina, pallor of the upper part of the left retina and mild edema at the margins of both optic disks. Our examination revealed normal vision and normal visual fields in the right eye, and an irregular loss of the lower half of the visual field of the left eye with central acuity of 6/10. The right fundus was normal, while the left showed moderate pallor of the upper half of the disk and considerable narrowing of an arteriole coursing above the macula.

In this case, there was apparently ischemia of the upper half of the retina with permanent damage to the ganglion cells.

CASE 2. A man, 50 years of age, was seen 6 months after loss of the lower half of the field of vision of the left eye. Vision in this eye was 6/20 and he was found to have sustained a loss of the lower half of the field. There also was a slight inferior contraction of the visual field of the right eye for small targets. There was considerable pallor of the left optic disk. The patient stated that he had lost the vision in the left eye suddenly. For the 18 months preceding this, he had had recurrent episodes of severe hematemesis and melena. The concentration of hemoglobin on examination at the clinic was 5 gm. per 100 cc. He had a duodenal ulcer. Six years later no change had occurred in his vision or in his visual fields.

Ischemia of the upper half of the retina probably accounted for this defect as in Case 1.

CASE 3. A man, 59 years old, had "doctored" for stomach ulcers and tarry stools for 25 years. Eighteen months previous to examination at the clinic he had had a severe hemorrhage from a duodenal ulcer, and he was totally blind for 4 days. Vision had returned gradually since that time. Visual acuity on examination at the clinic was found to be 6/30 in the right eye and 6/10 in the left eye. He had in the right eye only a 10 degree circular isle of vision between the fixation point and the physiologic blind spot. In the visual field of the left eye an irregular generalized concentric contraction left a residual central field of about 20 degrees in diameter. The optic disks were moderately pale and there was mild narrowing of the retinal arterioles. The retinal vessels were sheathed by glial tissue where they emerged from the disks.

It is probable that this patient had originally a bilateral ischemic optic neuritis.

CASE 4. A farmer, 59 years old, was seen 1 year after sudden loss of vision of the left eye followed in several days by loss of vision of the right eye. This had occurred about 1 week after recurrent severe melena which necessitated transfusions because of severe secondary anemia. Visual acuity on examination at the clinic was 1/60 in the right eye and he could see only moving objects with the left. His visual fields showed a residual isle of vision of about 60 degrees in diameter in the temporal field of the right eye and a

tiny isle about 10 degrees in diameter in the far temporal field of the left eye. Ophthalmoscopic examination revealed atrophy of rather severe degree of both optic disks.

Bilateral optic neuritis was probably the original lesion in this case, as in Case 3.

Case 5. A man, 53 years old, was seen 12 months after tonsillectomy which was followed by such severe hemorrhage that he was comatose for 2 days. Four days later, while at home, sudden weakness of the left arm, numbness of the left side of the body and loss of vision in the left eye developed. The visual defect decreased gradually. He was found to have mild hypertension, left hemihypesthesia, left-sided incoordination, ataxia, left-sided weakness, and choreoathetosis with a static tremor of the head and left arm. Visual fields showed a moderately incongruous left homonymous hemianopsia thought to be due to a lesion in the vicinity of the right lateral geniculate body. The ocular fundi showed only minimal arteriolar changes associated with hypertensive disease. The entire syndrome could be explained on the basis of thrombosis of the right thalamogeniculate artery. When the patient returned 3 years later, he was much improved from the neurologic standpoint. The visual fields had returned to normal except for a slight superior temporal depression in the field of the left eye. The optic disks were normal.

Mechanism Responsible for Lesions. It seems to be definitely established that loss of blood is the ultimate cause of this catastrophic loss of vision. The exact mechanism through which the loss of blood brings about the lesions in the retina, optic nerves or visual pathways, however, has been the subject of much discussion, and is still largely a matter of speculation. Many theories have been proposed. From the clinical standpoint, it is difficult to account for the varying disturbances in ophthalmoscopic and visual fields, the variations in degree of recovery, the usual delay between the occurrence of the hemorrhage and the onset of visual loss, the greater frequency of the syndrome in cases of repeated relatively small hemorrhages than in cases of a single massive hemorrhage, and the extreme rarity of visual loss after traumatic bleeding. Most writers seem to be unwilling to admit that anemia with resultant localized ischemia can explain all these variable reactions[5]. Von Graefe[18] in 1860 ascribed the loss of vision to hemorrhage into the nerve sheaths, for which theory there seems to be little evidence. Westhoff and Ziegler[54] in 1899 ascribed it to ischemic fatty degeneration of the optic nerve, and Hoffman[27] in 1899 to retrobulbar neuritis. Ulrich[51] suggested that the loss of vision was due to circulatory stasis in the retina. He thought that the loss of blood caused lowering of the blood pressure, which, in the presence of normal intra-ocular tension, resulted in slowing of the circulation through the central retinal vein. Wilbrand and Saenger[55] ascribed the visual loss to a changed consistency of the blood; Theobald[48], to thrombosis in the central artery.

Wolff[56] called attention to the faintness, giddiness and occasional loss of consciousness which are usually present at the onset of the visual disturbance and which are evidences of lack of oxygen. He reasoned that the constriction of the retinal arterioles, which is a characteristic and perhaps essential feature of the retinal lesions of quinine poisoning, is caused by the inhibiting action of quinine on the oxidizing power of protoplasm and of the blood. He suggested, therefore, that visual defects following loss of blood result from spasm of the retinal arterioles induced by anoxia. This theory was supported by Hartman and Parfonry[22]. They obtained improvement in vision by the administration of acetylcholine and thought that this indicated that vasoconstriction was the cause of the amblyopia. Duggan[8] also favored the assumption that arteriolar constriction

led to localized tissue anoxia. Røe[39] implicated 3 factors: ischemia, acidosis and the injudicious exposure of the eyes to light. Rosenstein[40] thought the loss of vision in some of the cases might be an early manifestation of multiple sclerosis. This is of interest in the light of Duggan's report[7].

Many observers, for example Groenouw[19] and Kümmell[29], have postulated that the action of a toxin was necessary in addition to the anemia, although Tidy[49], Tassman[45] and Langdon[30] were of the opinion that the anemia is probably the sole factor. Duke-Elder[9] stated that it is probable that something more than ischemia is necessary to produce the lesions. He suggested the "possible influence of severe hemoclastic shock or anaphylactic crisis or a toxemia due to profound hemolysis."

In the opinion of Scheffler[41], it is not possible to explain all the types of visual defects and ophthalmoscopic findings on the basis of a single mechanism. He divided the cases into 3 groups: those with retinal findings resulting from anoxemia from anemia; those with retrobulbar neuritis, and those with embolism or thrombosis of the central artery of the retina. The most recent writer on this subject, Locket[31], has stated that this variety of visual loss "would seem to occur when the blood-volume has returned to normal with the resulting fall in hemoglobin and plasma proteins. In view of our knowledge of the changes that occur in the blood after hemorrhage, it would seem that of all the changes, dilution of the blood by tissue-fluids is the one that is most likely to require hours or even days to occur, and would most closely parallel the onset of delayed amaurosis. Thus, in chronic illness there are 3 factors: anemia, low plasma proteins and low body reserves of protein."

The essential factor responsible for loss of vision following "distant" hemorrhage seems to be anoxia which affects in some cases the tissues of the retina, in others the optic nerves and in others the higher visual pathways. How this anoxia is brought about and why it affects different parts of the visual system in different cases is difficult to explain. It must be due to one or a combination of several different factors: deficiency of the oxygen-carrying capacity of the blood; inability of the tissues to utilize what oxygen is supplied, or insufficient flow of the oxygen-carrying components through the blood vessels due to embolism, thrombosis, lowered blood pressure or reduced blood volume. At present it seems improbable that any additional toxic factor is concerned in the loss of vision. At least, no such factor has been demonstrated. The anemia, reduction in blood volume, the subsequent dilution of the blood with tissue fluids, and the concomitant lowering of the plasma proteins as stated by Locket[31] seem to be primary considerations. To these factors might be added slowing of the blood stream in the retina associated with lowering of the blood pressure in the presence of maintained intra-ocular pressure which may result in relative ischemia of the retina or at times in actual thrombus formation in the central artery of the retina or in a branch arteriole. Anoxia usually causes dilatation of the arterioles. So the constriction of the arterioles seen in some of these cases is not likely to occur as a primary causative lesion but rather as a compensatory effort to retain normal capillary flow to the retina or else as a late development associated with the atrophy of the retina and optic nerve.

Loss of vision following massive hemorrhage must be fairly closely related to those well-known cases in which patients have had permanent loss

of portions of their visual fields subsequent to sudden lowering of the blood pressure, and to the complete loss of vision noted in some patients on whom intracranial surgery is done in the sitting position, as described by Walsh[32]. Perhaps the effect of gravity explains the far greater incidence of involvement of the superior portion of the retina.

Treatment. Treatment is usually directed toward correcting 2 conditions: the loss of blood and the lesion responsible for the bleeding. That it is important from the standpoint of preserving vision to control the bleeding is shown by the many cases in which further hemorrhage subsequent to the onset of loss of vision caused even further blindness. The use of transfusions promptly after severe loss of blood especially when the concentration of hemoglobin falls to less than 50%, is strongly indicated. We have found no case reported in the literature in which loss of vision followed adequate transfusion, except in those patients who awoke blind after coma. Striking improvement has been noted immediately after transfusions[16]. However, when loss of vision has occurred, immediate transfusion is no insurance against further loss, nor does it guarantee recovery[52]. Puppel[37] stated that in severe uterine bleeding followed by loss of vision the best treatment was immediate hysterectomy. He cited 2 cases in which improvement followed this procedure. Duke-Elder[9] stated that paracentesis of the eye may be used to lower the intra-ocular pressure in an attempt to improve the retinal circulation and restore vision. Early transfusion after severe hemorrhage is an important preventive measure against possible loss of vision. There probably is no very effective treatment once blindness has occurred.

The wisdom of the use of vasodilators immediately after the loss of vision is open to question. After bleeding has ceased, and the blood and blood pressure have returned to normal, vasodilators may be of value in stimulating return of function to any of the retinal ganglion cells or nerve fibers which have not undergone complete degeneration.

REFERENCES

(1) **Ballantyne, A. J.:** Tr. Ophth. Soc. U. Kingdom, **55,** 347, 1935. (2) **Barr, A. S.:** Am. J. Ophth., **17,** 396, 1934.

(3) **Carlini, V.:** Clin. ocul., **7,** 2353, 1906. Quoted by Moore, R. F.: Medical Ophthalmology, 2d ed., pp. 109-111. Phila., Blakiston, 1925. (4) **Clegg, J. G.:** Tr. Ophth. Soc. U. Kingdom, 55, 347, 1935. (5) **Coston, T. O.:** Internat. Clin., ser. **45,** 3, 252, 1935. (6) **Cox, R. A.:** Arch. Ophth., **32,** 368, 1944.

(7) **Duggan, W. F.:** Arch. Ophth., n.s., **16,** 380, 1936. (8) **Duggan, W. F.:** Am. J. Ophth., 26, 354, 1943. (9) **Duke-Elder, W. S.:** Retinal Ischaemia After Exsanguination. In: Textbook of Ophthalmology, vol. 3, pp. 2556-2560. St. Louis, C. V. Mosby, 1941.

(10) **Enriquez:** Tr. Ophth. Soc. U. Kingdom, **55,** 347, 1935. (11) **Esquirols:** Quoted by Kimmell, R.[29].

(12) **Fink, K.:** Zentralbl. f. Gynäk., **48,** 1188, 1924. (13) **Foerster:** Graefe-Saemisch Handb. d. Gesamt. Augenheilk., **7** (pt. 1), 73, 1876, Quoted by Groenouw, A.[19]. (14) **Fries, S.:** Klin. Monatsbl. f. Augenh., **14** (pt. 3), 3, 1876.

(15) **Goerlitz, M.:** Klin. Monatsbl. f. Augenh., **64,** 763, 1920. (16) **Goldfeder, A. E.,** and **Rapoport, K. N.:** Klin. Monatsbl. f. Augenh., **93,** 666, 1934. (17) **Gooch:** Quoted by Fuchs, Sigmund[14]. (18) **von Graefe, A.:** Arch. f. Ophth., **7** (pt. 2), 143, 1860. Quoted by Cox, R. A.[6]. (19) **Groenouw, A.:** Sehstörungen nach Blutverlusten. In: Graefe-Saemisch Handbuch d. Gesamten der Augenheilkunde, vol. 11 (pt. 1), pp. 304-314. Leipzig, Wilhelm Engelmann, 1911. (20) **Grout, G. H.:** Arch. Ophth., o.s., **43,** 234, 1914.

(21) **Harbridge, D. F.:** Am. J. Ophth., **7,** 192, 1924. (22) **Hartmann, E.,** and **Parfonry, J.:** Bull. Soc. d'Ophth. de Paris, p. 5, 6, Feb., 1934. Quoted by Cox, R. A.[6]. (23) **Heine, L.:** Die Krankheiten des Auges im Zusammenhang mit der inneren Medizin und Kinderheilkunde,

pp. 394-396. Berlin, Julius Springer, 1921. **(24) Hinton, J. W.**, and **Davis, D. A.:** Surg. Clin. No. Am., **29,** 317, 1949. **(25) Hippocrates:** Oeuvres Hippocratiques, Ed. by Littré, Vol. 7, p. 111. Quoted by Terson, A.[47]. **(26) Hirschberg:** Ophth. Gesellsch., Heidelberg, **10,** 53, 1877. Quoted by Kümmell, B.[29]. **(27) Hoffman, F. W.:** Klin. Monatsbl. f. Augenh., **21,** 171, 1883. Quoted by Theobald, Samuel[48]. **(28) Holden, W. A.:** Arch. Ophth., o.s., **28,** 125, 1899.

(29) Kümmell, B.: Die Sehstörungen nach Blutverlust. In Schiek, F. and Brückner, A.: Kurzes Handbuch der Ophthalmologie, vol. 7, pp. 62-68. Berlin, Julius Springer, 1932.

(30) Langdon, H. M.: Arch. Ophth., n.s., **10,** 99, 1933. **(31) Locket, S.:** Brit. J. Ophth., **33,** 543, 1949.

(32) Milew, A., and **Pierach, A.:** Münch. med. Woch., **79,** 1515, 1932.

(33) Pergens, E.: Ann. d'ocul., **115,** 5, 1896. **(34) Pincus, F.:** Arch. f. Ophth., **98,** 152, 1919. **(35) Pines, N.:** Brit. J. Ophth., **15,** 75, 1931. **(36) Pröll:** Diss., Jena, 1914. Quoted by Duke-Elder, W. S.[9]. **(37) Puppel, Ernst:** Monatschr. f. Geburtsh. u. Gynäk., **65,** 351, 1924.

(38) Rählmann: Fortschr. d. Med., **7,** 928, 1889. **(39) Roe, O.:** Acta ophth., **20,** 48, 1942. **(40) Rosenstein, A. M.:** Klin. Monatsbl. f. Augenh., **78,** 248, 1927.

(41) Scheffler, M. M.: Arch. Ophth., n.s., **29,** 449, 1943. **(42) Seese:** Quoted by Kümmell, B.[29]. **(43) Singer, K.:** Beitr. z. Augenh., **53,** 1, 1904. **(44) Stirling, J. W.:** Ophth. Rev., **23,** 219, 1904.

(45) Tassman, I. S.: The Eye Manifestations of Internal Diseases, pp. 417-423; 426. St. Louis, C. V. Mosby, 1942. **(46) Terrien, F.:** Arch. d'Ophth., **39,** 263, 1921. Quoted by Duke-Elder, W. S.[9]. **(47) Terson, A.:** Ann. d'oculistique, **159,** 23, 1922. **(48) Theobald, S.:** Am. J. Ophth., **16,** 145, 1899. **(49) Tidy, H. L.:** Brit. Med. J., **1,** 774, 1941. **(50) Traquair, H. M.:** An Introduction to Clinical Perimetry, 4th ed., p. 182. St. Louis, C. V. Mosby, 1944.

(51) Ulrich, R.: Arch. f. Ophth., **33** (pt. 2), 1, 1887.

(52) Walsh, F. B.: Clinical Neuro-ophthalmology, pp. 1046-1048. Baltimore, Williams & Wilkins, 1947. **(53) Watkins, C. H., Wagener, H. P.,** and **Brown, R. W.:** Am. J. Ophth., **24,** 1374, 1941. **(54) Westhoff** and **Ziegler:** Quoted by Theobald, Samuel[48]. **(55) Wilbrand, H.,** and **Saenger, A.:** Die plötzlichen Erblindungen nach Blutverlust. In: Die Neurologie des Auges, 3 (pt. 2): 907-923. Wiesbaden, J. F. Bergmann, 1906. **(56) Wolff, E.:** Tr. Ophth. Soc. U. Kingdom, **55,** 342, 1935.

(57) Zentmayer, W.: J. Am. Med. Assn., **59,** 1050, 1912. **(58) Ziegler, E.:** Beitr. z. path. Anat. u. Physiol., **2,** 57, 1888.

SURGERY

UNDER THE CHARGE OF

I. S. RAVDIN, B.S., M.D.

JOHN RHEA BARTON PROFESSOR OF SURGERY AND DIRECTOR OF THE HARRISON DEPARTMENT OF SURGICAL RESEARCH, UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PENNSYLVANIA

AND

C. G. JOHNSTON, M.S., M.D.

PROFESSOR OF SURGERY, WAYNE UNIVERSITY
DETROIT, MICHIGAN

PROGRESS IN SURGICAL DISEASES OF THE PANCREAS

BY JOHN M. HOWARD, M.D.

HARRISON FELLOW IN SURGICAL RESEARCH
PHILADELPHIA, PENNSYLVANIA

(From the Harrison Department of Surgical Research, Schools of Medicine, and the Surgical Clinics of the Hospital of the University of Pennsylvania)

PROGRESS in the field of surgery has now made possible exploration and resection of the pancreas with a margin of safety which was not possible a decade ago. As a result, the clinical, roentgenologic and laboratory aspects of pancreatic disease can now be compared with surgical rather than with autopsy observations. Clearer concepts of earlier stages and of milder diseases have therefore been possible. Now, with increasing accuracy, the clinician can make the diagnosis of pancreatic disease. Further advances in the diagnosis of chronic pancreatic diseases must await a further elaboration of diagnostic methods. The clinician is in need of, first, a pancreatic excretory or clearance test of function such as is available for the study of hepatic or renal disease, and secondly, a radiographic test of function and morphology comparable to the urogram and cholecystogram. Little progress has been made toward the development of either.

Endocrine System. PANCREATIC ISLET CELL TUMORS. Since 1924 when the hyperfunctioning islet cell tumors were postulated[13] the progress in their diagnosis and management has been exceedingly rapid. The preöperative diagnosis can now be made with reasonable certainty and definitive, curative treatment can be undertaken.

On a physiological basis, islet-cell tumors may be classified as either functioning or non-functioning, that is, they either do or do not produce insulin toxicity. So far, the non-functioning benign tumors seem of little clinical importance. Although 87 have been described by autopsy pathologists, only 4 of this group have been recognized and reported by surgeons or surgical pathologists[16]. The indications for operation on these patients were a palpable abdominal tumor (2 patients) and mass lesion on barium Roentgen-rays of stomach and duodenum (2 patients). Short term follow-up of these 4 patients indicates that excision of the tumor provides a satisfactory result.

A recent review of the literature[16] revealed that 211 functioning tumors had been resected. If the adenoma was found and removed, the result was al-

most uniformly excellent. However, the technical aspects of finding and removing the adenoma or adenomas is sometimes perplexing. For instance, 9 patients have been described in whom the adenoma was ectopic and in which, had the surgeon been content with a negative pancreatic exploration, the tumor would have been overlooked. Furthermore, the adenomas have been multiple in 43 patients (12.6%), so that the finding of a single adenoma is no indication that the exploration has been completed. All too frequently re-exploration or autopsy has shown that the surgeon has overlooked an adenoma. Again, if all tumors are removed, the patient is characteristically completely relieved and if the tumor is not removed, the patient dies of his hypoglycemia. The cause of his death, like the cause of his symptoms is due to the decreased concentration of glucose to the brain. The hypoglycemia and the resultant changes in the brain function are, in the earlier cases, the basis of the diagnostic Whipple triad: 1, Signs of hyperinsulinism; 2, An associated blood sugar below 50 mg. %; 3, Reversal and relief of symptoms by the administration of glucose.

If the adenoma is not removed and hypoglycemia allowed to recur or persist over a long period of time, irreversible damage to the brain results, the higher brain centers being damaged first, the older, more basic medullary centers being less sensitive to hypoglycemia[14].

Pathologists have classified these tumors on the basis of their histologic appearance and growth characteristics. First they describe the benign adenoma which makes up over 90% of the functioning and non-functioning tumors. Simple surgical excision does not result in recurrence and therefore is the preferable surgical procedure. Next, they describe a "suspiciously malignant" adenoma[12] which histologically appears malignant. Short term follow-up of these patients following surgical excision or enucleation shows no evidence of metastasis; so that, to date, their clinical behavior is that of a benign tumor. Thirdly, the pathologists describe the islet cell carcinoma in which metastases are demonstrable. Like the previous groups, hyperinsulinism may be an associated feature, but these patients die of the malignant effect rather than of the insulin effect[16]. Characteristically, this carcinoma is a slow growing tumor, and, of the 37 patients reported in whom metastasis have been demonstrated, several have lived for long periods of time, up to 6 years, without definitive treatment. The histologic and growth characteristics resemble the malignant carcinoid from which it must be distinguished.

Alloxan has no place in the management of islet cell tumors[24].

One of the major problems in the field of islet cell tumors and hyperinsulinism remains the physiological explanation and management of those patients, especially children, who have persistent hypoglycemia without convincing evidence of islet cell disease.

Resection of the pancreas in these patients, as would be expected, does not offer uniform relief. However, a number of patients with hyperplasia or adenomatosis of the islets have been relieved by subtotal pancreatectomy and such an operation must be considered, once the diagnosis of hyperinsulinism is made and a carefully performed exploration reveals no tumor.

The Exocrine System. ACUTE PANCREATITIS. The outstanding progress in the work with acute pancreatitis in the past 5 years has been the reduction in the mortality from this disease. In a university hospital, the mortality has been reduced from approximately 30%[17] to almost 3%[28] during this time. This

represents, in part, a true reduction in mortality and, in part, an increased accuracy in the diagnosis of the milder form of the disease.

The disease is clinically divisible into 2 forms; it is not yet clear whether they represent 2 diseases or separate stages of the same process. The milder form, edematous pancreatitis, is marked by edema of the pancreas with or without fat necrosis in the pancreas and adjacent structures. It is sometimes associated with an acute cholecystitis but often occurs independently. The pancreatic inflammation is reversible and the prognosis is therefore good. There is at present a question in the minds of most surgeons who are interested in this problem as to the treatment of preference[28]. Many surgeons prefer laparotomy for confirmation of the diagnosis and for decompression of the biliary tract by means of a cholecystostomy. This is designed, in part, to prevent reflux of bile into the pancreatic ducts. Othere surgeons have obtained good results by institution of a nonoperative peritonitis regimen combined with sympathetic (splanchnic and celiac) nerve blocks. Advocates of both the operative and the conservative regimens report low mortalities, which should now approach zero[28]. Neither group of therapists has shown conclusively that their treatment is specific and it may be that this form of the disease is self-limiting if infection is controlled and the patient is given supportive treatment.

Follow-up studies of these patients show that characteristically they have little impairment in pancreatic function[17].

The more severe form of the disease, hemorrhagic pancreatitis, constitutes only about 15% of acute pancreatitis but accounts for almost all of the present day mortality. Hemorrhage and necrosis of the pancreas are frequently massive. The inflammation is in part irreversible so that half or even the entire pancreas may slough. Operative drainage of such a pancreas is essential but technically difficult. Since operative drainage seems essential for this form of the disease, one of the outstanding problems facing the clinician is the differentiation between the milder and the more severe forms. As yet, there is no clear cut means of making this distinction prior to laparotomy.

Certainly the use of the antibiotics has been paramount in reducing the mortality from acute pancreatitis.

Although the reduction in mortality, that is the progress in treatment, has marked the greatest advance in the past few years, real progress is being made in understanding the pathologic physiology of the disease. It is now widely known that acute damage to the functioning pancreas results in an elevation of the amylase and lipase in the blood serum. The demonstration of an increased concentration of amylase in the serum requires approximately 2 hours and, when combined with acute abdominal symptoms, is diagnostic of acute pancreatitis. This test is now performed in the laboratories of most good hospitals. Such tests are the only specific means of making a definitive preoperative diagnosis, and in general, have proved very reliable[29].

These tests have also proved useful as experimental tools. For instance, recent observations show that damage to the pancreas, as in acute pancreatitis, results in a release of the pancreatic enzymes into the peripancreatic tissues and into the peritoneal exudate[15]. Animal experiments further demonstrate that the enzyme amylase is absorbed from the vicinity of the traumatized pancreas into the portal circulation and so reaches the peripheral circulation by way of the liver[18].

It has also been demonstrated fairly

convincingly that pancreatic ischemia plays a major role in the development of pancreatic necrosis and hemorrhage. For instance, Popper, Necheles and Russell[27] demonstrated that the injection of secretion or the ligation of the pancreatic duct of the dog produced edematous pancreatitis; but if at the same time the arterial blood supply was temporarily occluded, hemorrhagic pancreatitis occurred instead of the edematous type. This might be the explanation for the beneficial effect observed following sympathetic nerve blocks (paravertebral) in patients with acute pancreatitis.

Once the inflammatory process is reversed and the necrosis clears, healing of the pancreas begins. The pancreas heals mostly by fibrosis but there is evidence that regeneration also occurs. In experimental pancreatitis, the edema begins to subside during the first week and has cleared within 2 weeks. Meanwhile fibroblastic proliferation occurs and results in scarring[19]. Thus if little acinar tissue is destroyed and the reaction is minimal, the histological and functional recovery may be almost complete, but if repeated injuries to the pancreas occur the process may result in an atrophic, fibrotic gland designated by the surgeon as "chronic pancreatitis", though not a true inflammation.

Another syndrome, that of the pseudocyst, may result from the healing process. Massive necrosis or hemorrhage in the pancreas, as elsewhere in the body, may heal by fibrous encapsulation. Early exploration may therefore lead to the diagnosis of "encapsulated hematoma" whereas later exploration may demonstrate a "pseudocyst".

The etiology of the disease remains obscure and little progress has been made during the past decade in demonstrating the causative factors. Experimentally it has frequently been produced by the injection of bile into the pancreatic ducts or by an acute obstruction of the pancreatic ducts[22]. Neither factor has been conclusively demonstrated in clinical work. Alcoholism is frequently an associated factor[26]. Preliminary efforts to transmit the disease from person to person have been unsuccessful[15]. It must be remembered that acute pancreatitis may, in individual patients, be a manifestation of other diseases such as acute cholecystitis, common duct calculus, pancreatic duct calculus, carcinoma of the pancreas or ampulla of Vater, periarteritis nodosa, mumps, trauma, primary pancreatic hemorrhage, and possibly from penetration of a duodenal ulcer.

Acute Relapsing Pancreatitis. Of demonstrated clinical importance has been the recent appreciation of the syndrome of frequently recurring episodes of acute pancreatitis. This disease is closely allied to the problem of pancreatic calculi, for the two are frequently associated. Presumably calculi can produce a partial ductal obstruction which in turn may lead to pancreatitis. On the other hand, abdominal films taken at the time of repeated attacks of pancreatitis may initially show no evidence of lithiasis but over a period of years may show the appearance and progression of calcification in the ducts or throughout the pancreas (Fig. 1). In the absence of demonstrable pancreatic calcification serum enzyme determination is the only means of making a diagnosis of pancreatitis although a diabetic glucose tolerance curve and the demonstration of a diminished enzyme secretion into the duodenum are confirmatory evidence. The attacks of pain in the upper abdomen and back, nausea and vomiting may be severe but are diagnostically non-specific. A serum amylase test

should be done in the first 2 days of the attack and a negative test should be regarded inconclusive. Repeatedly, a failure to correctly diagnose this syndrome has lead to the assumption that the patient was psychoneurotic. Meanwhile, the patient, experiencing severe distress, may be driven to opiate addiction. This syndrome may well account for some of the patients who experience the "post cholecystectomy syndrome", that is, the original diagnosis of cholecystitis may have been incorrect or the symptoms may have been attributed to gallstones instead of to recurring attacks of pancreatitis.

Treatment of relapsing pancreatitis is necessitated by pain and not by the fear of developing a fatal hemorrhagic pancreatitis, although the latter has occurred[17]. Specific treatment, consisting of pancreatectomy or relief of a partial pancreatic ductal obstruction, has been associated with a high morbidity and has not proved entirely satisfactory. Relief of pain by division of the sympathetic pathways is a more conservative procedure, and, although this approach to therapy is indirect and carries certain inherent dangers, it is probably preferable to pancreatectomy[28]. Doubilet and Mulholland[7] report good results following division of the sphincter of Oddi, the rationale being to prevent the reflux of bile into the pancreas. Ligation of the

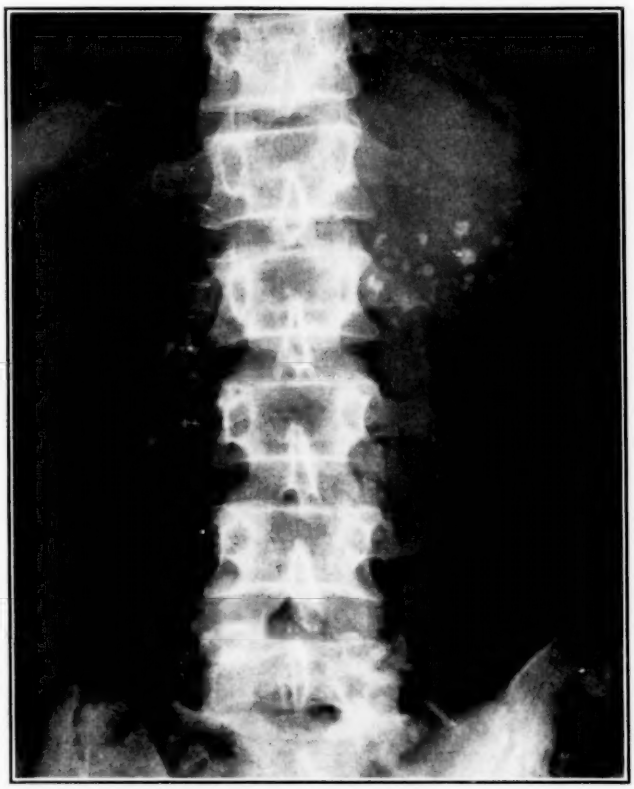


FIG. 1.—Pancreatic Calculi. Flat plate of abdomen showing deposits of calcium throughout the pancreas. (Courtesy Dept. of Radiology, Hosp. of the Univ. of Penna.)

pancreatic ducts with subsequent acinar atrophy may prove of value. To date, however, non-operative palliation seems preferable to surgical intervention unless the pain becomes intolerable.

Pancreatic Calculi. Progress in this disease has been marked chiefly by an increased and more widespread appreciation of its role in the production of acute and subacute abdominal pain. It is the pain and not metabolic disturbances which brings the patient to the physician. Often the pain is colicky in nature and not unlike "mid-abdominal or left sided gallstone colic".

Enzyme studies may be of some aid in demonstrating the secondary effects of the stones but the diagnosis of pancreatic lithiasis can only be made by a Roentgen-ray examination of the abdomen. The stones are composed of calcium carbonate and are therefore radio opaque. Radiolucent stones have not been demonstrated. Films show the stones across the upper abdomen at the level of T-12 to L-2 (Fig. 1). Barium studies of the duodenal loop may be of aid in localizing the stones and therefore in differentiating the doubtful ones from other retroperitoneal calcifications such as may occur in lymph nodes. Diffuse calcification throughout the pancreatic tissue may occur. The latter, in contradistinction to pancreatic duct stones, probably represents a healing reaction to previous pancreatic hemorrhage or inflammation. The diffuse calcification and pain may both be the result of pancreatic disease but it is difficult to understand how the diffuse calcification could produce pain.

The problem of treatment of pancreatic ductal stones is similar to that of the recurring pancreatitis. Specific therapy, that is, the incision of the duct and removal of the obstructing stones, has sometimes been unsuccessful due to the surgeon's inability to remove all calculi. If calculi remain after such an operation, pancreatic fistula is an all too frequent sequela. Further evaluation of surgical therapy[10] is needed, but any non-operative regimen appears of little value in controlling the patient's pain.

Pancreatic Cysts. The diagnosis of pancreatic cyst is being made with increasing frequency and accuracy by the radiologist and clinician when a retroperitoneal mass, characteristically producing minimal discomfort, is found to be displacing the stomach anteriorly.

Three types of solitary cysts are recognized. One, seemingly a retention cyst, is lined by ductal epithelium and is a "true pancreatic cyst". The second is a fibrous lined cyst which seems to be the result of encapsulation by scar tissue following hemorrhage or necrosis of the pancreas. This is the "false or pseudocyst" of the pancreas and seems to be the later stage of an encapsulated hematoma. The third is the rare cystadenoma which, as the name implies, is a combination of cyst and benign pancreatic adenoma. Only 28 surgically treated cystadenomas could be collected in a recent review[3]. All types of pancreatic cysts are best treated by complete excision rather than by marsupialization. Excision is now being performed with a rapidly decreasing mortality[28].

Pancreatic Carcinoma. In spite of much effort on the part of excellent surgeons, little real progress has been made toward curing the patient with cancer of the pancreas. Only cancer of the gallbladder or the body of the stomach can rival pancreatic carcinoma in progressing so far, so silently.

Several clinical observations have been of recent interest. In a series of 83 patients with pancreatic carcinoma, verified at autopsy, 76% of the patients felt pain; at autopsy nerve invasion

by the tumor was found in 84% of this subgroup[9]. A tendency to arterial and venous thrombosis has been described in association with pancreatic carcinoma[11].

Cancer of the ampulla manifests itself earlier, by intrinsic common duct obstruction, so that its diagnosis does not depend upon its spread as is the case with carcinoma of the ducts and acini. Carcinoma of the ampulla usually occurs in older people, but seems to grow more slowly. As it manifests itself earlier, it permits a more favorable outlook. Thus 5 year cures of ampullary carcinoma, after definitive surgery, should in the next few years prove fairly high, whereas five year cures of cancer of the rest of the pancreas should be reported because of their rarity. Pancreatic resection is providing relief for many patients for 1 to 3 years, however, and so should always be attempted[4].

Total pancreatectomy has led to a number of important physiological observations:

1. The exocrine function of the pancreas is not essential to life, although patients do better if a small amount of pancreas is left and the pancreatic duct is re-anastomosed to the bowel. Seemingly, the small bowel provides much of the digestive function of the pancreas. Following pancreatectomy the stools show a definite increase in the amount of undigested and consequently unabsorbed food, but with dietary supplements weight can be maintained. In a few patients, little or no change in the stools can be noted. Substitution therapy in the form of pancreatic enzymes or extracts administered orally has proved of only limited value. As would be expected, these patients fare much better than those with external pancreatic fistula in whom the loss of water and electrolytes results in a picture not unlike Addison's disease[25].

2. The insulin requirement in the "pancreatectomy diabetes" is unexpectedly low. The average daily insulin requirement of 14 patients after total pancreatectomy was 32 units[30]. Thus many patients with clinical, idiopathic diabetes require several times as much insulin for control of their blood sugar as do these patients. A few diabetic patients have required less insulin following total pancreatectomy[5].

3. The effect of pancreatectomy on liver function remains inconclusive in spite of the evidence of many investigators tending to involve lipocaic, which is described as an endocrine secretion of the islet cells necessary for hepatic lipid metabolism[8].

The Relation of the Pancreas to Diseases of the Gastrointestinal Tract. Duodenal Ulcer. The degree of acidity of the duodenal contents has been widely thought to be a factor in the production of duodenal ulcers. Most investigators have assumed that the increased acidity was the result of an increased acid production by the stomach. Reasoning that a decreased pancreatic secretion of alkaline fluid would tend to give the same resultant pH in the duodenum as an increased acid secretion by the stomach, Comfort and Osterberg[6] studied the pancreatic secretion in 10 patients with duodenal ulcer. They were unable to reveal any deviation from the normal. The pancreas, therefore, may not be at fault in the production of ulcers except following total pancreatectomy or subtotal pancreatectomy with ligation of the pancreatic ducts. The loss of its alkaline secretion may then be a predisposing factor to ulcer formation in the small bowel.

Meconium Ileus. Since Andersen's[1] classical article in 1938, fibrocystic disease of the pancreas has been widely

appreciated as giving rise to meconium ileus of the newborn, and pancreatic steatorrhea of later life, which is not a surgical condition (Wigglesworth[31]).

The background for fibrocystic disease of the pancreas is a single Mendelian recessive gene[23]. Histologically, the pancreas shows dilation of the ducts and acini secondary to either a congenital obstruction of the ducts or to plugging of the ducts by an eosinophilic secretion. Dilatation results in the formation of tiny cysts which leads to pressure atrophy of the acini and secondarily to fibrosis[31]. The fibrosis and cyst formation predominate in autopsy studies.

Meconium ileus of the newborn seems to be limited to patients with fibrocystic disease. It is characterized by intestinal obstruction which results from inspissation of meconium in the bowel. The level of the obstruction varies, Keith[21] stating that normally meconium reaches the ileocolic junction by the 4th month and the rectum by the 5th month of fetal life.

Windle[32] found that although the islet tissue begins functioning about the 3d month of fetal life, the proteolytic enzyme of the acini is not present until the 5th fetal month. The cause for the inspissation of the meconium has not been proved but a frequent explanation has been that since in fibrocystic disease enzymes are almost absent in the pancreatic secretion, the resultant decreased concentration in the bowel is responsible for the failure in hydrolysis of the intestinal contents and so in the prevention of the obstruction. Certainly, such a mechanism has not been clearly demonstrated.

Congenital Anomalies. Little has been added to the knowledge of congenital anomalies of the pancreas. Obstructing lesions of the duodenum by an annular pancreas, pyloric or duodenal indentations, as seen on barium studies, secondary to ectopic pancreatic nodules beneath the mucosa, and the presence of pancreatic tissue in Meckel's diverticulum have long been recognized. A survey of the world's literature revealed 106 cases of accessory pancreatic tissue in the stomach[20]. All of these ectopic deposits contain acini but only about one-third contain islet tissue. Of recent interest has been the descriptions of acute pancreatitis, islet cell adenoma and carcinoma in aberrant tissue[2]. A review of the clinical literature reveals no report of congenital absence of the pancreas.

Summary. Although recent progress in the understanding of pancreatic diseases has been considerable, the immediate frontiers of investigation center around the development of tests of function of the exocrine system including the development of a radiographic visualization of the excretory system, the inter-relationship of pancreatic and hepatic metabolism, the etiology of pancreatitis, the action of the circulating pancreatic enzymes in the serum and their activity when extruded into the peripancreatic tissues. A continued study of the role of the pancreas in diabetes is being made; and finally, there must be a continuing effort to improve the diagnosis and the treatment of the patient with pancreatic disease. Progress depends, in part, upon solving the many problems raised by assaying our progress to date.

REFERENCES

(1) **Andersen, D. H.**: Am. J. Dis. Child., **56**, 344, 1938.

(2) **Barbosa, J. J. DeC., Dockerty, M. B.,** and **Waugh, J. M.**: Surg. Gyn. and Obst., **82**, 527, 1946. (3) **Benson, R. E.,** and **Gordon, W.**: Surgery, **21**, 353, 1947. (4) **Brunschwig, A.**: Radical Surgery in Advanced Abdominal Cancer, Chicago, University of Chicago Press, 1947.

(5) **Brunschwig, A.**: Christopher's Textbook of Surgery, 5th ed., p. 1165. Philadelphia, Saunders, 1949.

(6) **Comfort, M. W.**, and **Osterberg, A. E.**: Gastroenterol., **4**, 85, 1945.

(7) **Doubilet, H.**, and **Mulholland, J. H.**: Surg. Gyn. and Obst., **86**, 295, 1948. (8) **Dragstedt, L. R.**: Ann. Surg., **118**, 576, 1943. (9) **Drapiewski, J. F.**: Am. J. Clin. Path., **14**, 549, 1944.

(10) **Eliason, E. L.**, and **Welty, R. F.**: Ann. Surg., **127**, 150, 1948.

(11) **Ferris, E. B. Jr.**, and **Ritterhoff, R. J.**: Ohio State Med. J., **41**, 437, 1945. (12) **Frautz, J. K.**: Ann. Surg., **112**, 161, 1940.

(13) **Harris, S.**: J. Am. Med. Assn., **83**, 729, 1924. (14) **Himwick, H. E., Frastg, J. P., Fazekas, J. F.**, and **Hadidian, Z.**: Am. J. Psychiat., **96**, 371, 1939. (15) **Howard, J. M.**: Surg. Clin. No. Am., December, 1949. (16) **Howard, J. M., Moss, N. H.**, and **Rhoads, J. E.**: Surg. Gyn. and Obst. To be published. (17) **Howard, J. M.**, and **Ravdin, I. S.**: Am. Practitioner, **2**, 385, 1948. (18) **Howard, J. M., Smith, A. K.**, and **Peters, J. J.**: Surgery, **26**, 161, 1949.

(19) **Ireneus, C.**: Arch. Surg., **42**, 126, 1941.

(20) **Keiser, D. Von:** Chirurgie., **19**, 154, 1948. (21) **Keith, A.**: Human Embryology and Morphology, 5th ed., p. 341, London, Edward Arnold, 1933.

(22) **Lium, R.**, and **Maddock, S.**: Surgery, **24**, 593, 1948. (23) **Lowe, C. U., May, C. D.**, and **Reed, S. C.**: Am. J. Dis. Child., **78**, 349, 1949. (24) **Lukens, F. D. W.**: Physiol. Rev., 28, 304, 1948.

(25) **Miller, J. M.**, and **Wiper, T. B.**: Ann. Surg., **120**, 852, 1944.

(26) **Paxton, J. R.**, and **Payne, J. H.**: Surg. Gyn. and Obst., **86**, 69. 1948. (27) **Popper, H. L., Necheles, H.**, and **Russell, K. C.**: Surg. Gyn. and Obst., **87**, 79, 1948.

(28) **Rhoads, J. E., Howard, J. M.**, and **Moss, N. H.**: Surg. Clin. No. Am., December, 1949.

(29) **Somogyi, M.**: Arch. Int. Med., **67**, 665, 1941.

(30) **Whipple, A. O.**: Ann. Surg., **124**, 991, 1946. (31) **Wigglesworth, F. W.**: Am. J. Med. Sci., **212**, 351, 1946. (32) **Windle, W. F.**: Physiology of the Fetus, Philadelphia, Saunders. 1940.

PROCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF DECEMBER 20, 1949

Ultraspectrophotometric and Chemical Studies on Extracts From Human Tumors. M. SPIEGEL-ADOLF, M.D., and M. E. SANO, M.D., C.Sc. (Depts. Colloid Chem. and Tissue Culture, Temple Univ.). The purpose of these studies is to reach a closer identification of the substances causing the optical absorption peak at about 2600A in tissue extracts and to correlate these results with morphological, and clinical findings (See Arch. Path. **44**, 307, 1947). NaCl extracts were made of 100 specimens of human origin after mechanical fragmentation of the frozen tissue and centrifugation. The optical studies were made with a Beckman Quartz photoelectric spectrophotometer; micro-Kjeldahl methods were used for the determination of the total and non-protein nitrogen. Ascorbic acid was determined according to the method of Robinson-Stotz.

In a group of 12 tumors of the gastrointestinal tract, 9 malignant growths showed an average extinction coefficient (E_{20}^{260}) of 2.6256. One inflammatory and 2 benign tumors showed values of $E_{20} = 1.2766$, 1.2652, and 0.7620 respectively. In 7 breast tumors, 1 carcinoma (intraductal) and a benign adenoma with many inflammatory cells gave the highest E values, next came a scirrhous carcinoma. Optical absorption of the other benign tumors were markedly lower, but had nevertheless a good parallelism with the histological findings and the NPN values. In all cases the latter were sufficient to cover the amount of nucleic acid showing an optical absorption similar to the one of the extracts.

In 22 brain tumors the E_{10}^{260} values varied between 0.5916 — 3.470. In tumors of similar structure E values and histological findings were in agreement.

Among 35 lymph nodes a good parallelism between the number of cells and extinction values was noticeable. But while lymph nodes with prevailing cancer cells had an absorption peak at about 2600A, the hyperplastic lymph nodes showed a shift of their peaks to about 2550A. Neither the ascorbic acid content of our tumor extracts nor their protein concentration were significant enough to warrant a correction.

Reflexes From the Perfused Lungs of Dogs Breathing Spontaneously. DOMINGO M. AVIADO, Jr., M.D. (Nat'l Inst. of Health Post-Doctorate Res. Fellow), and T. H. LI, M.D. (Lab. of Pharmacol. Univ. of Penna.). The demonstration that veratridine causes reflex apnea by acting on receptors in the lungs (Aviado, D.M., and Pontius, R.G., Am. J. Med. Sci., **218**, 115, 1949) offers a tool for further investigation of presso-reflexes and chemo-reflexes from the pulmonary circulation. The existence of pulmonary vascular receptors has been demonstrated by convincing histological and oscillographic methods. Almost all reported physiological experiments were on dogs and cats with open chests and the reflexes were due to changes in pressure alone, and arising from lungs with the veins ligated.

Part or whole of the left lung of

anesthetized dogs (morphine and chloralose) was perfused with blood from a donor dog. The effects of individually changing oxygen content, CO_2 content, and the pressure of the blood in the pulmonary artery and pulmonary vein were studied. Veratridine was found satisfactory to test the functional acceptability of each preparation.

Although veratridine can still reflexly inhibit respiration and circulation through apparent chemoreceptors in the perfused lung, no chemo-reflex sensitive to changes in blood oxygen and CO_2 was demonstrated. Pulmonary congestion causes a reflex drop in systemic blood pressure and a reflex inhibition of respiration. Like the veratridine receptors, the presso-receptors appear to be in the pulmonary venous side and are connected centrally by the ipsilateral vagus.

The in vitro Secretion of Phenol Red by Mammalian and Amphibian Renal Tissue Slices. ROBERT H. PAINTER, A.B., ETHEL L. WILLIAMS, HAROLD M. PECK, M.D., and KARL H. BEYER, M.D., Ph.D. (Dept. of Pharmacol., Sharp and Dohme, Glenolden, Pa.). Phenol red is secreted into the proximal convoluted tubules when thin slices of frog kidney are oxygenated in Ringer's Solution containing small amounts of the dye (Forster, R.P.: Science, **108,** 65, 1948). A technique has been developed whereby the same observations have been extended to mammalian tissues. An aerated modified Krebs-Ringer-bicarbonate solution incubated at 37° C has been used. Two methods for maintaining the constant temperature have been used: 1, the microscope stage incubator; 2, the Warburg flasks and constant temp. bath. Colored photomicrographs demonstrate phenol red concentrated in the lumina at 15 to 30 min. Carinamide and a group of similar compounds block this secretory mechanism reversibly.

Using the Warburg flasks and constant temperature bath, manometric studies of the tissue respiration can be made simultaneously with observations of dye secretion in the proximal convoluted tubules. This provides an enzymatic approach to the study of the renal transport mechanism.

The Enzymatic Components of a Renal Secretory Mechanism. VIRGIL D. WIEBELHAUS, Ph.D., R. H. PAINTER, A.B., R. L. KEMP, B.S., and KARL H. BEYER, Ph.D., M.D. (Dept. of Pharmacol., Med. Res. Div., Sharp and Dohme, Glenolden, Pa.). Secretion of phenol red by the proximal tubules of guinea pig renal cortical slices has been studied enzymologically with the objective of defining the mechanism of this transport system. Employing the technique of Beyer, *et al.* (to be published) the visual observation at the completion of the manometric incubation periods permits a study of the correlation between physiologic function and the enzymatic components required for maintenance of the function. Aerobiosis is essential for active secretion of phenol red. Phenylhydrazine (5×10^{-3} M), cyanide (5×10^{-4} M), benzoquinone (1×10^{-3} M), mercuric chloride (1×10^{-3} M), 3,4,dinitrophenol (5×10^{-5} M) and phloridzin (5×10^{-3} M) all inhibit the secretion of phenol red although the latter two did not decrease the rate of oxygen uptake. This demonstrates that a system of coupled oxidation/phosphorylation must function adequately in order to maintain the prerequisites for this secretory process.

Inhibition by phenylhydrazine, phloridzin and dinitrophenol has been shown to be partially reversible, although it is difficult to demonstrate

reversibility because the secretory capacity of the slices can be maintained for only a limited period at the temperature of incubation. Carinamide. 4' carboxyphenylmethanesulfonanilide inhibits this secretion at levels which have no effect on oxygen uptake. The inhibition by carinamide is apparently specific for the definitive component of this secretory process since 1, the inhibition is readily reversible; 2, the compound does not inhibit the reabsorption of glucose or arginine and does not affect the secretion of N-methylnicotinamide; 3, there is no correlation between the systemic toxicity of carinamide homologues and their relative potency as inhibitors of renal tubular secretion.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia 4, Pa. Articles are accepted for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

MANUSCRIPTS should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. ILLUSTRATIONS accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. The recommendations of the American Medical Association Style Book should be followed. REFERENCES should be numbered and at the end of the articles arranged alphabetically according to the name of the first author and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers).

RETURN POSTAGE should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

100 REPRINTS will be supplied gratis. Covers will be omitted on all articles. Orders of additional reprints will be supplied in multiples of 100.

BOOK REVIEWS AND NOTICES

A Manual of the Penicillia. By Kenneth B. Raper, Principal Microbiologist, and Charles Thom, Collaborator, U. S. Dept. of Agriculture, Peoria, Ill. Technical Assistance and Illustrations by Dorothy I. Fennel. Pp. 875; 171 ills. Balt.: Williams & Wilkins, 1949. Price, $12.00.

This is a complete reorganization of the earlier monograph, *The Penicillia*, by Thom. It is designed to identify, and as a guide to, the literature on the activities and significance of *Penicillia*. The first part (5 chapters) is a general discussion on *Penicillia* and penicillin, including methods of cultivation and preservation of *Penicillia*. The second part (10 chapters) is the manual proper; and the third part (4 chapters) contains reference material and a topical as well as a general bibliography. It will be a valuable book for the laboratory worker interested in any aspect of these molds. H. M.

Modern Practice in Psychological Medicine. 1949. Edited by J. R. Rees, M.D., Tavistock Clinic, London. Pp. 488. New York: Paul B. Hoeber, 1949. Price, $10.00.

This book, edited by an eminent English psychiatrist, is intended for students of medicine and for general practitioners rather than for specialists in psychiatry. As stated in the foreword, technical details of methods of investigation and treatment which require specialist experience are not given. The chapters have been written by 29 different Authors, almost all of whom are British. Chapter 21, entitled "Psychotherapy" (J. R. Rees, the Author) contains impressions and information which will be especially helpful to all those who want to be of assistance to other people. W. P.

A Year with Osler, 1896-1897. By Joseph H. Pratt. Pp. 209; 5 ills. Balt.: Johns Hopkins Press, 1949. Price, $4.00.

Few people realize the value that historians and biographers attach to authentic records of every day events. The mere fact that the circumstance is a familiar one that happens frequently is sufficient reason to explain why it is robbed of any significance at the time of its occurrence. This leads one to assume, therefore, that it cannot be of any importance to future generations. And yet the meticulous transcripts that Boswell made of conversations formed, in large part, the basis for one of the great biographies. Medical students usually discard the fragmentary notes of clinics and lectures as soon as the immediate need for them has passed. Dr. Pratt preserved his, and their particular interest lies in the fact that as he states in his "Preface", "they are made up almost entirely of the exact words of the Master".

The principal subject of this small volume is preceded by an introduction in the form of a short biographical sketch, composed very largely of personal recollections of Sir William Osler. A preface follows in which the writer outlines in a few pages the organization of the Medical Clinic at The Johns Hopkins Hospital as it appeared to him when he studied under Dr. Osler during the winter of 1896 and 1897.

The main body of the book is composed of notes made at Dr. Osler's informal conferences given in the dispensary and the more elaborate clinics held in the amphitheatre. The notes are brief, almost always dated, and consist of an outline of the patient's history followed by a verbatim record of Dr. Osler's comments. It is characteristic that these discussions often contain references to medical history, personal recollections and some telling epigrams which made these clinical demonstrations such fascinating exercises. Typhoid fever and pneumonia loom large amongst the great variety of conditions that were presented, and the appendix contains a list of the cases of these two diseases that were seen by the students during the course of the year.

The book furnishes an impression of Osler's method of teaching and it sketches in sharp lines the personality of a great master. A debt of gratitude is due Dr. Pratt for having made and preserved these records which are now made available to the medical public.

W. L.

The Neurosis of Man. By Trigant Burrow, M.D., Ph.D., Scientific Director, Lifwynn Foundation. Pp. 428; 26 figs. New York: Harcourt, Brace, 1949. Price, $7.50.

In the foreword of this book, we learn that Freud once asked someone, "Does Burrow think he is going to cure the world?" Dr. Burrow's response was, "I most certainly do." He, like most thoughtful people, is concerned with the possibility, or perhaps inevitability, of another world war. He advises "phyloanalysis"—an analysis of the phylo-organism of man. The book considers the

question as to how man as a social organism can be led to reverse his own social habituations. Perhaps some people will find that it contains some of the answers to some of the problems of today. W. P.

SURGICAL MANAGEMENT OF VASCULAR DISEASE. By GERALD H. PRATT, M.D., Assoc. Clin. Prof. of Surgery, New York Univ. Pp. 496; 181 ills., 2 in color. Phila.: Lea & Febiger, 1949. Price, $10.00.

THIS is an unusually well balanced monograph, concise and easily readable. The author has drawn from his extensive experience in the treatment of vascular lesions. Whereas treatment is emphasized, theoretical, anatomical, diagnostic and pathological aspects are also included. It is divided into sections on the nomenclature of vascular diseases and obtaining the patient's history, diseases of the venous, arterial and lymphatic systems, surgery of the heart and appropriate techniques useful in the management of vascular abnormalities. This book is recommended for reading and reference for all who treat patients with vascular diseases. H. Z.

FACTORS OF EVOLUTION. By I. I. SCHMALHAUSEN, Formerly Member Academy of Sciences of U.S.S.R. Pp. 327; 42 ills. Phila.: Blakiston, 1949. Price, $6.00.

THE subject matter of this valuable book, drawn from the diverse fields of morphology, ecology, paleontology, systematics and genetics, is synthesized into a philosophy of evolution emphasizing the stabilizing factors of natural selection. In the Preface by the Author and the Foreword by Th. Dobzhansky the extensive subject matter of the volume is briefly related to concepts advanced by other authorities. This subject matter includes individual variability as a source of historic change in organic nature, the dynamics of the historic variability of populations, elementary processes of the variation of an organism and of its historical development and the rate of evolution and the factors determining it. The 13 page bibliography should be useful to students, teachers and research investigators wishing to delve more deeply into special aspects. P. W.

IRON METABOLISM AND ITS CLINICAL SIGNIFICANCE. By A. VANNOTTI, M.D., Prof. of Internal Medicine, and A. DELACHAUX, M.D., Lector Univ. of Lausanne. Translated by ERWIN PULAY, M.D. Pp. 267. New York: Grune & Stratton, 1949. Price, $6.50.

THIS monograph was first published in German in 1942 by Schwabe of Bâle, Switzerland. In his preface to this first English translation Dr. Vannotti states that several chapters of the original 1942 edition have been supplemented and recast and a third part added for the benefit of practicing physicians. For the student of iron metabolism this monograph will be a useful reference book. The bibliography naturally contains more references to German literature than comparable compilations published in this country. Many of the references are prior to 1942, the date of the original publication. The work presented is authoritative and scholarly. The most useful purpose of this translation seems to be that of introducing and making available to English speaking readers much of the older literature of iron metabolism published in Continental Europe. The Reviewer does not believe that the practical considerations (Part 3) are sufficiently helpful to general practitioners to justify purchase of this monograph. T. F-H., Jr.

BLOOD TRANSFUSION. Edited by GEOFFREY KEYNES, M.D., Emeritus Surg., St. Bartholomew's Hosp., London. Pp. 574; 109 ills. Balt.: Williams & Wilkins, 1949. Price, $12.50.

THE stated purpose of this book by British authors is to compile all essential current knowledge concerning blood transfusions and related subjects in one volume. There is an excellent historical review by the Editor, Geoffrey Keynes. The technical sections are written by 7 collaborators. All of the chapters have been carefully and thoughtfully prepared, and the writing is uniformly good. A special effort has been made to include all developments of importance up to 1949. In the discussion of most topics the world literature is reviewed, and there are complete lists of references at the end of the chapters. This book compares favorably with other recent texts covering this field. It may be recommended without reservation. C. K.

TREATMENT IN PROCTOLOGY. By ROBERT TURELL, M.D., with a Chapter on Psychosomatic Problems by LOUIS LINN, M.D. Pp. 248; 85 ills. Balt.: Williams & Wilkins, 1949. Price, $7.00.

THIS monograph is to be commended for applying the many advances made in medical science during the last decade to the specialty of anorectocolonic diseases. As well as discussing sulfonamide and antibiotic therapy, anesthesia, and diets and nutrition, the Author includes chapters on such special

topics as proctology in geriatrics and pediatrics, psychosomatic proctological disorders, and a summary of drugs and physical equipment useful to the proctologist for diagnostic and therapeutic procedures. Pre- and postoperative care is discussed. The chapter on the management of pruritus ani is helpful.

The references at the end of each chapter include the more recent literature. The many illustrations are excellent, with some unusually good colored photographs.

The emphasis of the Author is on treatment in all its phases as related to proctology. This book should be useful to medical students, internes, residents and general practitioners who wish a brief up-to-date handbook that is written by one obviously qualified in his field.

N. M.

BLOOD AND PLASMA TRANSFUSION. By MAX M. STRUMIA, M.D., Sc.D.(Med.), Assoc. Prof. of Pathology, Univ. of Pennsylvania, and JOHN J. MCGRAW, JR., M.D., Instructor in Pathology. Pp. 497; 124 ills. Phila.: F. A. Davis, 1949. Price, $7.50.

THIS text deals with the details of operation of a blood bank, the preparation and preservation of plasma, the preparation of crystalloid solutions, the indications for transfusion of blood and plasma, etc. The authors are qualified to discuss the subject because of their experience in civilian and military laboratory medicine. They are to be commended for the simple lucid style of presentation which makes the subject matter readily understood by both physician and technician. Even the simplest technique, such as venipuncture, is given in detail. The text is adequately documented with illustrations of procedures, equipment, and charts which rationalize therapy with blood and plasma. Clinical pathologists and laboratory technicians will find this book well worthy of their attention.

R. N.

HISTOPATHOLOGY OF THE SKIN. By WALTER F. LEVER, M.D., Instructor in Dermatology, Harvard Med. School. Pp. 449; 221 ills., 8 in color. Phila.: J. B. Lippincott, 1949. Price, $10.00.

TEACHERS of cutaneous histopathology have for a long time felt the need of a concise, well-illustrated and up-to-date compilation of this subject. Because previous source books have been too large, poorly illustrated, out of print, or written in a foreign language, an individual teacher had to devise his own collection of collateral reading for his students. Lever has produced a concise, readable, and for the most part well-illustrated text, which places emphasis upon essential histological features with particular reference to those diseases in which histologic examination is of diagnostic value. This book's 20 chapters cover the gamut of dermatologic diseases together with a brief discussion of some general topics including embryology and histology of the skin, laboratory methods, and morphology of the mesodermal cells.

On the whole, the subject is presented in an entirely acceptable manner. In addition to the Author's own ideas, there are ample, especially English language, literary references for the more interested reader to consult. There are, however, certain parts to which the Reviewer would take exception; for example, even granting that an aversion to cutaneous punches for obtaining biopsy specimens is unjustified, one can not pass without comment Lever's statement that, "as a rule, it is inadvisable to include normal tissue in the biopsy specimen because improper sectioning by the technician may result in only normal skin being seen in the section." This objection can easily be avoided by simple directions to the laboratory worker, and the advantages for orientation yielded by having normal skin in the specimen are demanded by competent pathologists.

H.B.

MENTAL HYGIENE IN PUBLIC HEALTH. By PAUL V. LEMKAU, Assoc. Prof. of Public Health, Johns Hopkins Univ. Pp. 396; 9 figs. New York: McGraw-Hill, 1949. Price, $4.50.

THIS is the first book that has been published on the subject of preventive psychiatry in the field of public health. It is a welcome contribution to medical literature and will be especially appreciated by those who are concerned with public health work, psychiatry, and general medicine. The organization of the book is largely that of a course in mental hygiene. The summary at the end of every chapter is a helpful arrangement. Perhaps the most informative chapter is "The Attack on the Problem" (Chapter 5), which describes the efforts made in different sections of the United States and Canada to attack mental hygiene problems through the medium of public health agencies.

W. P.

PROGRESS IN ALLERGY. Vol. 2. Edited by PAUL KALLOS, Helsingborg, Sweden. Pp. 356; 50 figs. New York: Interscience Pub., 1949. Price, $7.50.

THIS volume presents an excellent cross section of the recent advances in the field of allergy from the fundamentals of immunochemistry to the more practical aspects of therapy of such clinical conditions as status

asthmaticus, allergic dermatoses, and so on. The multiple contributors include authorities in both Europe and United States. It is an advanced treatise and while of great value to the advanced student or specialist in the field of allergy, is not suitable for the neophyte in the field nor for undergraduates. A brief introduction and the last 62 pages of the text are in German, the remainder in English. It would seem more practical to publish in one language, that of the country where the volume is to be offered. M. M.

HEMORRHAGIC DISORDERS. By PAUL M. AGGELER, M.D., Ass't Clinical Prof. of Medicine, and S. P. LUCIA, M.D., Prof. of Medicine, Univ. of California. Pp. 112; 126 ills. Chicago: University of Chicago Press, 1949. Price, $10.00.

THIS monograph, partly in color, is a beautiful hand-drawn, practical outline which is well-organized, accurate and up-to-date. The technical procedures necessary for the diagnosis of hemorrhagic diatheses are given in detail. Individual diseases are covered with a decided emphasis on therapy. The quality of the printing, drawings, and diagrams and the unnecessarily large number of illustrations are responsible for the high sales price. The brief descriptions of the subjects and the small amount of theoretical material make the work of value for students and internists but unsuitable for hematologists. D.S.

FUNDAMENTALS OF OTOLARYNGOLOGY. By LAWRENCE R. BOIES, M.D., Clinical Prof. of Otolaryngology, Univ. of Minnesota. Pp. 443; 184 ills. Phila.: W. B. Saunders, 1949. Price, $6.50.

THIS is an intelligently organized, well-written, competently illustrated book. The clinical chapters mostly represent the oto-rhinolaryngologic opinion of today that has a factual basis. Admittedly incomplete as a reference work, numerous references are offered as a guide to the reader whose interest moves him to further inquiry. The book will serve adequately the every-day needs of undergraduate medical students and physicians who are not specialists. N. F.

RADIOLOGIC EXPLORATION OF THE BRONCHUS. By S. DI RIENZO, M.D., Chief, Radiology Dept. Institute of Cancer, Univ. of Córdoba, Argentina. Translated by TOMAS A. HUGHES, M.S. Foreword by RICHARD H. OVERHOLT, M.D. Pp. 332; 466 ills. Springfield, Ill.: Charles C Thomas, 1949. Price, $10.75.

IN this monograph a leading roentgenologist presents the results of studies by his meticulous technique in the entire gamut of bronchial lesions. The Author's ideas on bronchial "dynamism" are unique; particularly intriguing is his impression (strikingly illustrated) that coughing is primarily a local "active ejaculation of *(sic)* the bronchial wall". Throughout, much attention is directed to the "bronchial sphincters" and to their postulated roles in the etiology of broncho-pulmonary disease. The discussion of technique stresses "spot" roentgenography during bronchial filling and "serial" exploration, meaning detailed observation of the mode of filling successively of the larger bronchi, their finer branches, and finally, of the alveoli. The interesting concept is advocated that asthma is manifested as a localized, segmental narrowing of bronchial branches with failure of alveolar filling. The illustrations are numerous and of excellent quality. A regrettably large number of typographical errors mars the translation.

This important work should stimulate interest in more detailed bronchographic studies in clinical cases with particular attention to bronchial physiopathology. H. S.

CHYMIA. ANNUAL STUDIES IN THE HISTORY OF CHEMISTRY. EDGAR F. SMITH MEMORIAL COLLECTION, UNIV. OF PENNSYLVANIA. Edited by TENNEY L. DAVIS (HENRY M. LEICESTER has succeeded the late Mr. Davis), an Editorial Board, and an international group of Consulting Editors. Pp. 189; 20 ills. Phila.: Univ. of Pennsylvania Press, 1948. Price, $3.50.

PERPETUATED by an endowment by Edgar Fahs Smith's widow, the Memorial Collection is now able to carry out his unfulfilled hope to establish a journal devoted to the subject. This first of a series of annually appearing bound volumes contains 14 studies, mostly in English. Though including but little of direct medical concern—an article on calomel is the only one in this volume—we are glad to welcome this important outlet for chemical historical studies. E. K.

ISOTOPIC TRACERS AND NUCLEAR RADIATIONS, WITH APPLICATIONS TO BIOLOGY AND MEDICINE. By WILLIAM E. SIRI, Univ. of California. Pp. 653; 136 figs. New York: McGraw-Hill, 1949. Price, $12.50.

IN the rapidly developing field of radioactivity there is need for a current handbook of theory and practice which summarizes and brings to date concepts and advances. This book admirably fits the need. The text is

conveniently subdivided into 3 sections: isotopes and nuclear radiations, methods and instruments, and biological and medical applications of isotopes. There are full discussions of nuclear structure, radioactivity, counters, internal dosimetry, safety measures, and instruments for the production of isotopes, with numerous useful illustrations, tables, and graphs. The section on the biological and medical application of isotopes is of necessity incomplete, but representative. Such a wealth of factual material is present in all sections that the handbook can serve as an invaluable reference source for the investigator. I. Z.

BRIDGES' DIETETICS FOR THE CLINICIAN. Edited by HARRY J. JOHNSON, M.D., F.A.C.P., formerly Ass't Clinical Prof. of Medicine, New York. Post-Graduate Medical School. 28 contributors. 5th ed. Pp. 898. Phila.: Lea & Febiger, 1949. Price, $12.00.

THIS latest revision brings up to date a volume which has long been regarded as one of the most useful practical texts in the field of nutrition. All of the former features are retained, including the exceptionally complete appendix consisting of extensive food tables, adequate low cost diets, specific organic, vitamin, mineral and other contents of foods, glossary of vitamin terms and definitions. There has been added a new chapter on Folic Acid together with complete revision of all the chapters dealing with diseases and their dietary management. This is a comprehensive and highly useful volume. K.E.

NEW BOOKS

Children in Conflict. By MADELINE L. RAMBERT. Translated by JEAN PIAGET, Prof., Institute J. J. Rousseau, Geneva, Switzerland. Pp. 214; 14 figs. New York: Internatl. Univ. Press, 1949. Price, $3.25.

A MOST interesting book on how a practicing psychoanalyst treats young children, with especial reference to her utilization of puppets and drawings.

It is not the sort of therapy which the general physician will be qualified or anxious to undertake but it will help explain to him some of the types of methods used by his psychoanalytic colleagues. W. P.

Streptomycin, Its Nature and Practical Applications. Edited by SELMAN A. WAKSMAN, Ph.D., Rutgers Univ. Pp. 618; 95 ills. Balt.: Williams & Wilkins, 1949. Price, $10.00.

THIS book, the work of 58 contributors, emphasizes the clinical application of streptomycin. There are, however, short sections on the biological and chemical aspects of streptomycin, its antibacterial and pharmacologic properties, and its application in veterinary medicine and agriculture. Since streptomycin was isolated in 1943 approximately 1800 publications have appeared concerning it. While there are selected references at the end of each chapter, no effort was made to present complete bibliographies. Reference is made to a more complete bibliography, "The Literature on Streptomycin, 1944-1948" published previously. Of the many clinical applications which are discussed, emphasis is placed on the use of streptomycin in tuberculosis. Laboratory workers and clinicians will find this book very useful. H. M.

Synopsis of Hernia. By ALFRED H. IASON, M.D., Instructor in Anatomy, New York Medical College. Pp. 500; 97 ills. New York: Grune & Stratton, 1949. Price, $6.50.

IN this book the author has revised and summarized his earlier volume (Blakiston, 1941). It represents a ready source of much information valuable especially to students and younger surgeons. The various types of hernias are lucidly described as to etiology, management and prognosis. The section dealing with complications and dangers of inguinal and femoral hernias is excellent.

Aside from minor errata and occasional use of somewhat unfortunate phraseology, the book is a good contribution to the field and to the practicing surgeon's library. J. H.

Tuberkulose-Lexikon für Arzte und Behörden. VON DR. MED. HABIL. WILHELM ROLOFF. Pp. 372. Stuttgart: Georg Thieme Verlag (New York: Grune & Stratton, 1949). Price, $4.50.

THIS is a useful dictionary type of encyclopedia concerning tuberculosis. Adequate general references are given. It is written in clear and understandable language. Adequate and simple definitions are presented. An especially desirable feature consists of 10 pages devoted to words commonly used in the discussion of tuberculosis and diseases of the chest and their equivalents in German, English, French, Italian and Spanish. L.C., Jr.

Electrocardiographic Technique. By KURT SCHNITZER, R.T.,M.D. Pp. 96; 46 ills. New York: Grune & Stratton, 1949. Price, $3.50.

THE technique of recording the generally accepted precordial and extremity leads and the common causes of unsatisfactory tracings comprise half the material of this manual. These are supplemented by simple descriptions of heart and circulation, string and amplifier types of instruments, and special procedures and devices about which the Author thinks that the electrocardiographic technician should be informed. The format, style and illustrations are good; the latter sometimes overprofuse. The book can certainly be recommended for nurse or technician and contains much helpful material for physicians inexperienced in the routine recording of electrocardiograms. J.S.

Annual Review of Biochemistry. Vol. 17. Edited by J. MURRAY LUCK, *et al.* Stanford, Calif.: Annual Reviews, 1949. Price, $6.00.

THIS 18th volume of the series continues the record of excellence of its predecessors in reviewing some 23 selected fields of investigation. The subjects reviewed yearly are: biological oxidations;

proteolytic and non-oxidative, non-proteolytic enzymes; carbohydrate chemistry; chemistry of the lipids, amino acids and proteins, nucleoproteins, nucleic acids and derived substances, neoplastic tissue; metabolism of the lipids, protein and amino acids; phosphorus compounds; carbohydrate metabolism; mineral metabolism; chemistry of the hormones; vitamins; nutrition; metabolic inhibitors, and mineral nutrition of plants. Topics not reviewed regularly include chemistry of antibiotics; insect biochemistry; nitrogenous constituents of plants, and organic acids of plants.

H. V.

The Mental and Physical Effects of Pain. By V. C. MEDVEI, M.D., Assoc. Chief. Ass't, Endocrine Clinic, St. Bartholomew's Hosp., London. Pp. 59. Edinburgh: E. & S. Livingstone, 1949. No price given.

SOME all too brief historical remarks on pain precede a mature consideration of the 2 parts of this interesting study.

Acute Laryngotracheobronchitis. By A. HARRY NEFFSON, M.D. Pp. 197; 17 ills. New York: Grune & Stratton, 1949. Price, $5.00.

NEW EDITIONS

A Boy Grows Up. By HARRY C. MCKOWN. 2d ed. Pp. 333; illustrated. New York: McGraw-Hill, 1949. Price, $2.40.

THIS is a complete revision of the 1940 edition with new chapters, illustrations and bibliography. Designed to help teen-age boys, it contains a considerable amount of information which may be helpful not only to them but to their parents as well. It is concerned with the everyday situations and problems of the average Junior and Senior High School boy rather than with those of the poorly adjusted or emotionally disturbed boy.

W. P.

Laboratory Manual for Principles and Processes of Pharmacy. By HENRY M. BURLAGE, Ph.D., Dean and Prof. of Pharmacy, Univ. of Texas, JOSEPH B. BURT, Ph.D., Dean and Prof. of Pharmacy, Univ. of Nebraska, and L. WAIT RISING, Ph.D., Prof. of Pharmacy, Univ. of Washington. 2d ed. Pp. 271. New York: McGraw-Hill, 1949. Price, $3.00.

THIS manual gives a good comprehensive coverage of pharmaceutical manipulations, being designed to accompany the text of the same name. The review questions contained in the manual are good. However, any benefit to be derived from the manual as a source of reference following completion of the prescribed course is very limited.

J. M.

Unipolar Lead Electrocardiography. By EMANUEL GOLDBERGER, M.D., Adjunct Physician, Montefiore Hosp., New York. 2d ed. Pp. 392; 221 ills. Phila.: Lea & Febiger, 1949. Price, $7.50.

Digitalis and Other Cardiotonic Drugs. By ELI RODIN MOVITT, M.D. 2d ed. Pp. 245; 19 ills. New York: Oxford University Press, 1949. Price, $5.75.

Clinical Diagnosis by Laboratory Examinations. By JOHN A. KOLMER, M.D., Prof. of Medicine, Temple University. 2d ed. Pp. 1212; 93 ills. New York: Appleton-Century-Crofts, 1949. Price, $12.00.

Physiology of the Uterus. By S. R. M. REYNOLDS, M.A., Ph.D., Carnegie Institution of Washington, Baltimore. 2d ed. Pp. 611; 55 figs. New York: Paul B. Hoeber, 1949. Price, $12.50.

Mongolism and Cretinism. By CLEMENS E. BENDA, M.D., Instr. in Neuropathology, Harvard Med. School. 2d ed. Pp. 316; 104 ills. New York: Grune & Stratton, 1949. Price, $7.00.

The Clinical Examination of the Nervous System. By G. H. MONRAD-KROHN, M.D., Prof. of Medicine, Royal Frederick Univ., Oslo. 9th ed. Pp. 459; 131 ills. New York: Paul B. Hoeber, 1949. Price, $5.00.

Stedman's Medical Dictionary. Edited by NORMAN BURKE TAYLOR, M.D., with ALLEN ELLSWORTH TAYLOR, D.S.O. 17th ed. Pp. 1361. Balt.: Williams & Wilkins, 1949. Price, $8.50 (without thumb index, $8.00).

THIS edition appears under the same editorship as the 16th edition, after a 3 year interval "as thoroughly revised as previous editions." Nevertheless, it appears, after superficial examination, to be less completely up to date than is the new Gould, for instance. In comparison with the 15th edition (see Am. J. Med. Sci., **204**, 597, 1942), the chief innovation is a lengthy (28 page) root-word list in the preliminary section on medical etymology.

E. K.

A Textbook of Physiology. Edited by JOHN F. FULTON, M.D., Sterling Prof. of Physiology, Yale Univ. 16th ed. Pp. 1258; 556 figs. Phila.: W. B. Saunders, 1949. Price, $10.00.

THIS edition is up-to-date and broadened in scope. Sections on muscle, nerve, special senses and nervous system occupy 40% of the book; they are magnificently done and probably provide the best text in any language. The Editor deserves congratulations. Lack of integration between sections by 29 authors sometimes occurs. Thus Poiseuille's law is described in detail 3 times. However, for the most part there is little to criticize.

H. B.

Physiology in Health and Disease. By CARL J. WIGGERS, M.D., Prof. of Physiology, Western Reserve Univ. 5th ed. Pp. 1242; 280 ills. Phila.: Lea & Febiger, 1949. Price, $10.00.

IT is 5 years since the publication of the last edition of this text, so that the current edition contains many new features including a whole chapter on the physiological basis of psychosomatic medicine. There are some minor misprints but the high standard of previous editions is maintained.

C. W.